The American Journal of DIGESTIVE DISEASES

An Independent Publication

DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION

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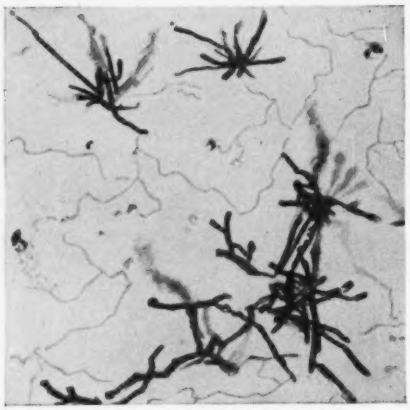

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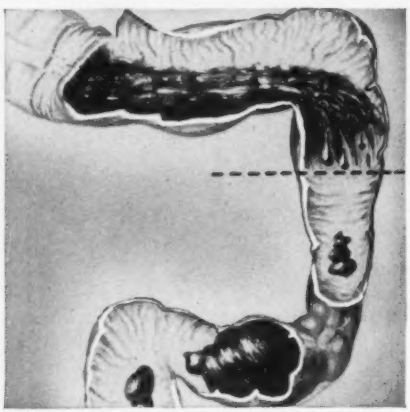

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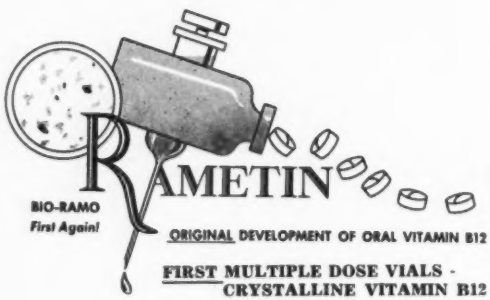

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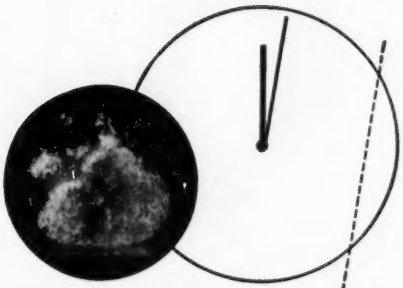

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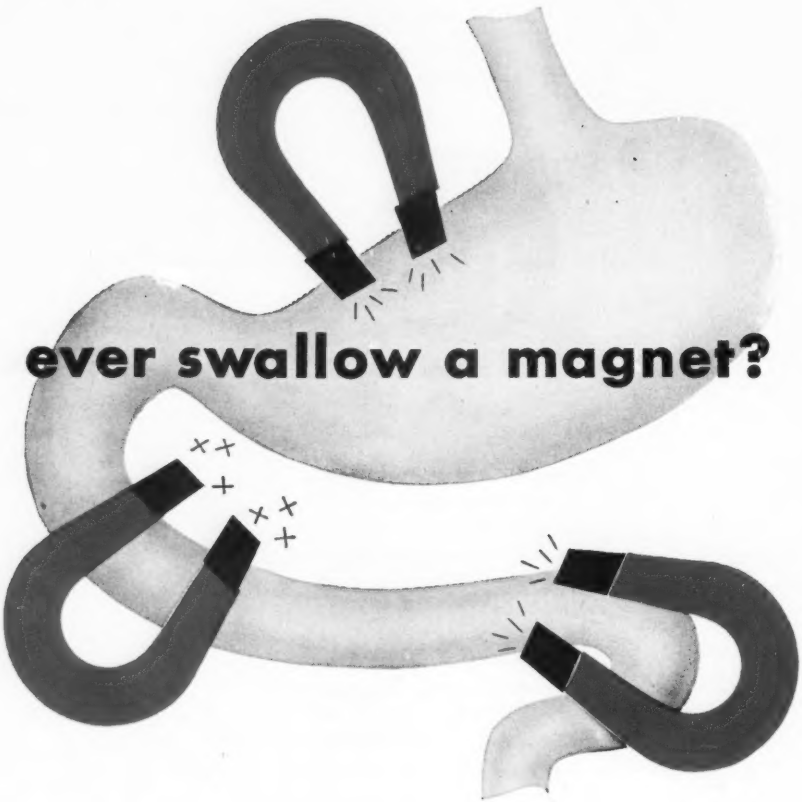

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1 Spears, M. M., and Pfeiffer, M. C. J.: Gastroenterology **8**:191 (Feb.) 1947.
2 Marks, J.: Review of Gastroenterology **16**:82 (Jan.) 1949.
3 Weiss, J.: Review of Gastroenterology **15**:826 (Nov.) 1948.
4 Wilkinson, J., and Martin, J.: Physical-Chemical Aspects of the Action of Anion Exchange Resins in Biochemical System. Arch. Biochem. **10**:205, 1946.

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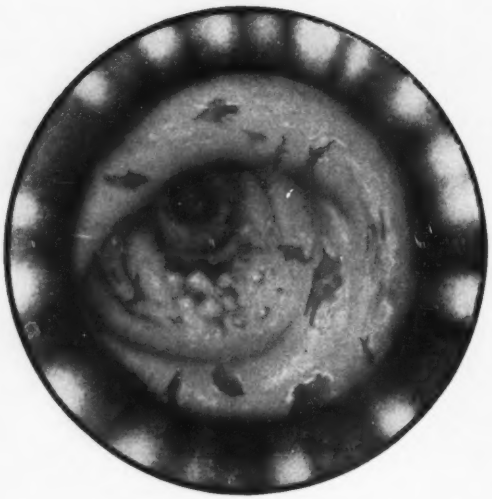

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1. Dowling, H. F., et al.: Ann. New York Acad. Sc. 53:433 (Sept. 15) 1950.

2. Sayer, R. J., et al.: Am. J. M. Sc. 221:256 (March) 1951.

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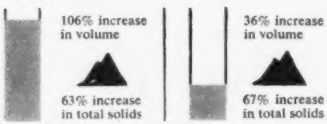

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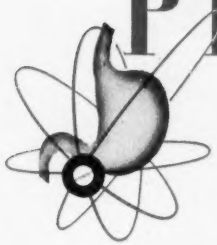

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MODERN CONCEPTS OF THE PHYSIOPATHOLOGY OF DIABETES MELLITUS

JOSEPH H. BARACH, M. D., F. A. C. P. Pittsburgh, Penna.

AS AN acceptable definition of the etiology of diabetes, in the light of present day knowledge, we may say that the diabetic state is induced by alterations in the flow of hormones from the Pituitary, Adrenals, Thyroid or Pancreas, with resulting disturbances of sufficient magnitude to disrupt normal functioning of enzyme metabolism. Be it disturbance in the hexokinase reaction or whatever its true nature, this in turn leads to altered oxidation and storage of glucose and glycogen, and ends in diabetes.

Should anyone at this time be overawed by the intricacy and ingenuity of present day accomplishment in this field of experimental research, I would call your attention to the work of Zuelzer in 1907 (3), in which he enunciated the fact that there is a mutual antagonism between the adrenals and the pancreas. And, that the glycosuria which follows pancreatectomy, is due to the diabetogenic action of what he termed "epinephrine."

This "epinephrine" which we may now be calling Adreno Corticotropic Hormone, said he, "is diabetogenic in the absence of sufficient internal secretion by the pancreas." How right all of this seems today—43 years later.

It may also be recalled here, that Zuelzer, Dohrn, and Marxer, in 1908 (66), actually produced an insulin which, unfortunately for them and the diabetic patient, was not sufficiently pure for therapeutic use.

PRESENT DAY CONCEPTS OF EXPERIMENTAL DIABETES

The diabetic syndrome is being studied intensively and extensively; new facts and new viewpoints are being presented in rapid succession; and these, sooner or later, are bound to be correlated and aligned in such a way as to form a pattern that will lead to a clarification of its Pathological Physiology.

Towards this end, the following outline is offered as representing the acceptable facts, as of today, with the expectation of better and final answers in the future.

CORRELATING EXPERIMENTAL AND CLINICAL DIABETES

Having presented the case for diabetes as it is induced in the experimental animal today, the important question is, "How far does this apply to human diabetes?" One's first impulse is to say that it should go all the way, and that, if experimental diabetes does not reflect underlying causes of human diabetes, then we have spent a good deal of time, and high endeavor, on something akin to shadow boxing—if I may use that undignified term.

This is all important, inasmuch as a number of outstanding workers, within the year, have expressed the thought, or implied, that there is as yet no general agreement among investigators in this field as to whether any known means of causing glycosuria in the laboratory animal is closely allied to the cause of diabetes mellitus (15) (107). Such declarations, which I am sure are not thoughtless utterances, call for a reconsideration of what, at least some of us believed to be established clinical fact.

Submitted July 23, 1951.

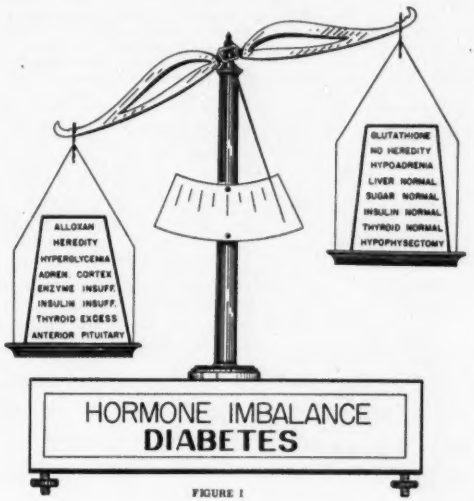

FIGURE 1

CLINICAL DIABETES

With this in mind, I therefore present a group of cases that tend to affirm and confirm the unity and similarity of experimental findings with that of clinical diabetes. I present these cases here, only to make our discussion more complete, since these represent the every day experience of clinical workers.

In the present state of our knowledge, concerning the occurrence of diabetes in patients with manifestations of other endocrinopathies, it is not always an easy matter to say, whether the diabetes or the associated endocrine disorder was primary or secondary.

It should always be remembered that, while a patient's diabetes is discovered on a certain day, the impending diabetes of that patient, in all likelihood, has been on the way for at least five to ten years, according to our experiences, and during that time, it might very well have been uncovered by careful clinical study. And, it is equally true, that the diabetes may have been on the way, even before birth, where heredity plays its part as it does in at least 45% of the cases.

It should also be recalled, that in a disease like Acromegaly, the evolution of the disease may begin anytime after adolescence, and comes into full development after the 40th or 50th year has been attained.

A simple enumeration of these associated diseases

TABLE I

EXPERIMENTAL DIABETES

	Diabetogenic	*Anti-Diabetogenic*	*Beta Cells*	*Glutathione*
Pancreas Reference 1-15	Pancreatectomy Anti-Insulin or Hyperglycemic factor	Hypophysectomy Normal Beta cells Hypoglycemic factor	Degranulation, vacuolz, Cell destruction—70%	Glutathione formation maintained.
Ant. Pituitary 16-31	Excess Hormone Enzyme Inhibition Insulin resistance	Hypophysectomy Hypopituitarism	Over stimulation Degranulation—Destruction	A. P. E. excess reduces glutathione.
Ardenal cortex 32-48	Excess Hormone Insulin resistance	Cortex removal Hypoadrenia	Cellular fatigue Degranulation Insulin resistance	Removal of cortex disturbs enzymes; glutathione falls.
Thyroid Gonadal 49-57	Post-pancreatectomy Insufficiency or excess	Normal Normal	Over stimulation Degranulation—Destruction	Indirect effects
Liver Enzymes 79-81	Insufficiency Enzyme deficiency Cortico steroids	Normal	Influence glucose tolerance and glycogen storage.	Maintains enzymes
Hyperglycemia 58-65	Excessive or oft repeated—reduces tolerance.	Lowering glycemia restores Beta cells.	Degranulation—exhaustion delayed hexokinase reactions.	Glutathione falls after A. C. T. H.
Insulin 66-78	Insufficient amount Insulin resistance Hyperglycemic factor Excess	Hexokinase reaction	Cystine+Methionine+ Enzymes make insulin. Beta cells store insulin.	Glutathione contains cystine. Glutathione increase in blood.
Alloxan 88-100	Toxic High fat diet	Glutathione Large doses	Destroys Beta cells	Glutathione falls; antag. to alloxan poison.
Uric Acid Purins 109-110	Increased after A. C. T. H.	Normal	Degranulation follows excess	Glutathione falls
Glutathione 101-108	Insufficiency	Cystine—Methionine protective	Protects Beta cells	Mostly in R. B. C. Maintains enzymes
Ascorbic acid 111-117	Deficiency With Alloxan	Not	Ascorbic acid deficiency injures Beta cells	Antagonistic
Heredity Obesity 118	Yes Post-pancreatectomy	Not		
Emotional trauma	Acting Through hormones			

would be about as follows: Diabetes with disturbances in the Pituitary gland, Diabetes with adrenal lesions, Diabetes with alteration in the Thyroid gland, and Pancreatic Diabetes.

Taken as a whole, these endocrinopathies as we see them in the Clinic, actually have their counterpart in diabetes of the experimental animal, as the following case histories will show.

CASE I

DIABETES WITH PITUITARY DISEASE—ANTERIOR LOBE

Case No. 30090
Date—7/29/48

E. L.—Male, age 53, Acromegaly; Post adolescent hyperpituitarism, Anterior lobe, progressive over the past ten years. Sella Turcica enlarged and deformed, contracted visual field, and polycythemia. The clinical syndrome in this patient was complete. The skeletal growth of these patients is in breadth—horizontally—in contrast to patients with preadolescent hyperpituitarism, who grow longitudinally, even to gigantism. The diabetes in this patient was not of the "fulminating" type as commonly seen in pancreatic diabetes. This patient, for a time, showed marked insulin resistance, with no more effect from 160 units than 25 units per day. He died of coronary occlusion at age 54 after 5 years of diabetes.

As one studies this type of case, an interesting question presents itself. What is the modus operandi of this horizontal growth as compared with longitudinal growth? What stimuli determine the growth in the soft tissue of the tongue for example, that produces the extraordinary symmetrical enlargement of this organ, and above all, what is the relationship of acromegaly to diabetes, and should these cases be classified as true diabetes?

CASE II

DIABETES WITH POST LOBE HYPOPITUITARISM OR HYPOPHYSEAL DISEASE, AND POSSIBLE DIABETES INSIPIDUS.

Case No. 37831
Date—3/1/49

H. Z.—Male, age 68, normal weight, 130—present weight 90 pounds. (Simmond's cachexia?) Was mildly diabetic at 62, omitted insulin 5½ years and for a time was considered to

be a case of arrested diabetes. Insulin started again recently, and was given up to 530 units daily by his family physician, prior to hospitalization. Showed urinary acetone daily, which we believe was due to liver glucose exhaustion from hyperinsulinism. Blood CO_2 52 Vol.%. Blood Sugars ranged between 538 and 284 mgm. Insulin was reduced progressively from 530 to 80 units per day, and yet the blood sugar level continued unchanged. X-ray of Sella Turcica showed enlargement and thickened post clinoid processes. Clinically this was a case of dyspituitarism with insulin resistance. The persistent polyuria—4000-5000 cc. daily, suggested diabetes insipidus. There was, however, no striking benefit from insufflation of pituitary powder or solution.

CASE III

DIABETES WITH CUSHING'S DISEASE—PITUITARY BASOPHILIC ADENOMA—ADRENO-CORTICO INVOLVEMENT

Female, age 40, obesity, sex disturbances, virilism, marked hypertension, painful areas over face. Patient illustrates close relationship between Pituitary, Adrenals, Gonads, and Diabetes. Was refractory to Insulin.

CASES IV-V

DIABETES OF BEARDED WOMEN. ADRENO GENITAL SYNDROME: MASCULINIZATION, PSYCHIC AND SOMATIC CHANGES.

Case No. 12942
Date—12/1/42

Mrs. A., at age 23 weighed 135, at age 27 weighed 213. Diabetes found at 26. BP 140/100. Polycythemia, insensitive to insulin. Laparotomy: *Adrenal Cortical Tumor:* 2 small nodules. Hyperchromatic, granulated cells, and vacuolization. These granulated cells are believed to be responsible for virilism. Poor response to insulin. In some patients the psychic changes are as marked as the somatic. "Greet from afar, the beardless man and the bearded woman" say the French.

CASE VI

DIABETES. HYPERTENSION. POSSIBLE PHEOCHROMOCYTOMA. HYPERTHYROIDISM; THYROIDECTOMY

Case No. 17490
Date—8/18/49

Female, age 58, glycosuria, hypertension and menopause at 50. Hyperthyroidism, past five-six years. Before operation weighed 110 pounds. Four months later weighed 140 pounds. BP 250/100—after operation 170/70. Since then, at times up to 200/90. Diabetes under complete control. Less insulin required (10 units) since operation. Clinical picture suggests hyperadrenalism or possible pheochromocytoma with diabetes.

CASE VII

DIABETES INDUCED BY A. C. T. H.

This type of induced diabetes is well exemplified by the studies of Conn and others (43) (44).

"Studies Upon Mechanisms involved in the Induction with Adrenocorticotropic Hormone of Temporary Diabetes Mellitus in Man."

CASE VIII

DIABETES WITH HYPERTHYROIDISM; EXOPHTHALMIC GOITER, HYPERTENSION.

Case No. B-449
Date—3/20/50

Mrs. S., age 45. Hypertension 13 years duration. Diabetes 4 years. At 18, weighed 140, at entrance to hospital weighed 110—three weeks later weighed 120. Insulin 55 units; good control. Thiouracil proved to be upsetting. Lugol's Solution effective: min. X tid. Pre-operative insulin dosage—60 units daily. Thyroidectomy was performed. Insulin requirement was doubled during the post-operative period; but the pre-operative dose was restored after the operation.

CASE IX

Case No. B-292
Date—3/20/50

Mrs. B.—age 75, height 5'3", weight 100 pounds. Diabetes 3 years duration. Adenomatous goiter—hyperthyroidism. B.M. rate 46% plus. Extensive calcification of aorta, blood vessels and lungs. Considerably increased need for Insulin during post-operative period. Good recovery.

It should be stated here, that these patients were operated on for their destructive hyperthyroidism and not to ameliorate their diabetes, although we have seen diabetes disappear for several years after thyroidectomy.

DIABETES WITH ADDISON'S DISEASE

"Clinical and Metabolic study of 11-dehydro-17-hydroxy-corticosterone acetate (Kendall Compound E) in hypertension, Addison's Disease and Diabetes Mellitus."

"Addison's Disease and Diabetes Mellitus in Three Patients" (43) (44).

DIABETES WITH PHEOCHROMOCYTOMA

The hyperglycemia with pheochromocytoma is known to cause irreversible changes in Beta cells, leading to diabetes.

These are outstanding examples of combined or co-incidental clinical endocrinopathies with diabetes, and if not true diabetes, then we must consider them carbohydrate metabolic disturbances—presenting the picture of clinical diabetes.

PRESENT DAY PROBLEMS IN RESEARCH AND THEIR CLINICAL IMPLICATIONS

Hyperglycemia

Evidence is accumulating to establish the importance of hyperglycemia per se, as a cause of diabetes. The diabetogenic factors enumerated in Table I, give support to this concept.

Haist, Campbell, and Best (59) have emphasized the advisability of resting the insulin producing cells to prevent or delay the onset of Diabetes.

Lukens, Dohan and Wolcott (61) produced diabetes by inducing continuous hyperglycemia, and then ameliorated that diabetes by allowing the blood sugar to drain off, as a result of phloridzin glycosuria with its lower blood sugar levels (62) (63) (64) (65).

Houssay has shown that in the experimental animal, three small meals are better than one large one with its resulting hyperglycemia; and that a high animal fat diet increases the tendency to diabetes more so than a high Carbohydrate or high Protein diet (114) (116).

The clinical implications of these observations are clear enough. Prevention or control of hyperglycemia, as may be attained by optimal diets, adequate insulin dosage, and avoidance of all known hyperglycemic factors, whatever their origin.

Beta Cells

Beta cells are not normal in 87% of pancreases of diabetics. The average insulin content of pancreas in the diabetic is 25% of normal: approximately 50 units per pancreas (70) (73). It should also be realized that a histologically normal appearing Beta Cell, may be functionally inadequate, and that such inadequacy may be caused by functional inefficiency, fatigue from overwork, and toxic effects of one kind or another. Any of these may produce shortage of insulin and faulty enzymatic functioning (11) (12).

Histologic study of the pancreas of one of our diabetics, one of the first four or five to receive insulin in Toronto, (December, 1922) revealed the presence of only an occasional islet, the cells of which were markedly atrophic. Nor were there any evidences suggesting that there had been more islets and that they had undergone fibrosis or hyalinization. To all appearances, this patient, not having sufficient insulin producing tissues, developed diabetes at age 45. Given insulin—40 to 50 units daily—he was sustained for 28 years, and died at age 73 with carcinoma at the head of pancreas.

Hypoglycemia, continued for three to eight months, induced by excess insulin, will produce a pancreas that is low in insulin content. (13). A long continued high fat diet, particularly so if it is high in animal fats, causes degranulation of Beta Cells. (12-116).

According to Bell, Beta Cell granules represent insulin or the precursors of insulin. Beta Cells synthesize insulin out of certain amino acids, such as Cystine and Methionine. Insulin contains 12% Cystine; and Cystine is a constituent of Glutathione. Since these are amino acids, it has been suggested that adequate protein diet for the diabetic, would seem to be of the order of first importance. The cystine content of the diabetic's serum is being studied at the present time, but as yet without definite conclusions (102) (105) (106). Young believes that the alteration seen in Beta Cells, leads to disturbed enzymatic action (15).

Induced Diabetes

Hypophysectomy is followed by atrophy of the adrenals; and administration of anterior lobe extracts restores the adrenal cortex. Long's studies have revealed the relationship between Pituitary and Adrenals, from which such substances as A. C. T. H. originate.

Ingle and others, demonstrated the glycosuric effects of 17 and 11 cortico sterones (33) (34) (35) (36). According to Conn (43) (44) administration of A. C. T. H. depresses endogenous A. C. T. H., and when A. C. T. H. is discontinued, deficiency of A. C. T. H. results. Following this, pituitary adrenal activity is inaugurated, cortico-sterones are released, and glycosuria follows, as a result of enzymatic disturbances which disrupt normal Carbohydrate metabolism. Cortical hormone effect is not limited to Carbohydrate metabolism; Protein metabolism is also affected. The action and reaction pattern here, resembles that of Insulin.

Insulin

A number of questions have arisen concerning the hexokinase reaction. Stadie and Haugaard have noted that the hexokinase reaction in muscle or kidney extracts of diabetic rats do not vary from that of non-diabetic rats, and they have not been able to show that insulin acts with other hormones in a homogeneous system. Insulin becomes bound with muscle tissue and that combination is influenced by other hormones (84) (85) (86) (87).

Broh-Kahn and Mirsky (71) (72) believe that insulin exerts its influence on the glycogenolytic cycle of the liver, by a mechanism other than direct effect on the enzyme systems, presumed by some, to be responsible for the entire series of transformations involved in these cycles.

An interesting and important observation is, that Insulin introduced into the blood stream, causes temporary hypoglycemia, suggesting that exogenous insulin may have a temporary depressing effect on the Beta Cells. This might well be of clinical importance, in so far as overdosage with insulin is concerned.

Stilbene, a chemical substance, has been reported as being capable of increasing the production of endogenous insulin; (77) (78) this would certainly be a step forward in the treatment of the diabetic, if it could be utilized to that end.

PREVENTION OF DIABETES AND EXPERIMENTAL RESEARCH AS OF TODAY.

It is recognized clinically that 90% of diabetics go through a period of pre-diabetic obesity. Following pancreatectomy, it has been noted that animals go through a period of obesity. Do these two facts point in the same direction? Does hypoinsulinism, under certain conditions, tend to produce obesity? Is the pre-diabetic obesity actually a part of the disease, as I have strongly suspected for many years?

Uric acid can be broken down to dialuric acid. Dialuric acid can be oxidized to alloxan. Do errors in the Uric acid metabolism produce alloxan? Can alloxan be formed in the body, and if so, under what conditions?

Alloxan destroys Beta Cells. Glutathione prevents and inhibits the destructive action of alloxan. Does glutathione have a place in the therapy of diabetes? (102) (104)

Beta Cells synthesize insulin out of amino acids such as Cystine and Methionine (105). Insulin contains 12% Cystine. Methionine protects against diabetes (Houssay.)) Can a liberal protein diet, one containing a plentiful supply of amino acids, supply Cystine and Methionine, thus providing insulin making materials?

There are goiterogenic and anti-goiterogenic foods. Are there Pituitary and Anti-Pituitary and Adreno and Anti-Adrenogenic foods?

Vitamin C deficiency lowers glucose tolerance—how? (112) (114) (115) High cocoanut and corn oil in diets protects animals against alloxan diabetes. High lard diets, continued for some time, are conducive to Beta Cell injury (116). Are these observations applicable in clinical Medicine?

Thiouracil

In the experimental animal, Thiouracil seems to exert a protective action against diabetes. This is believed to be due to increased Glutathione in the tissues of the animal (102) (107). Every one of these observations seems to open up new fields for study, with the hope of supplying answers to important questions. The answers may not come easily, and certainly, they will not come all at once.

SUMMARY

All considered, the available facts at this stage in our knowledge of diabetes, both experimental and clinical, point clearly to hormonal imbalance between the pancreas, pituitary, adrenals and thyroid. Whatever alters the smooth and normal functioning of the pancreatic hormone, disturbs sugar production and sugar utilization primarily, and protein and fat metabolism secondarily at the various intermediary stages. Whatever the resulting nutritional disturbances may be, they are fortunately, in a large measure, corrected by the administration of insulin. This we see from day to day.

It is true that certain fundamental questions still have to be answered, particularly those pertaining to intermediate metabolism; but increasing knowledge concerning the hexokinase reaction, phosphorylation, and the part played by Pyruvic acid, seems to be leading us in the direction of a more complete understanding of this disease.

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SPONTANEOUS CHOLECYSTODUODENOSTOMY: REPORT OF A CASE OF LONG STANDING*

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CHOLECYSTODUODENOSTOMY may be the result of an operation to shunt bile around an occluded common duct, or it may occur spontaneously. The latter is usually the result of a cholecystitis and cholelithiasis with erosion of a stone or stones into the duodenum, though less frequently carcinoma of the gall bladder and a penetrating duodenal ulcer may be the underlying cause. In a review of the subject, Garland and Brown (1) showed that 90 cases of spontaneous

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internal biliary fistulas had been reported to 1942. Since then Waggoner and Le Mone (2) reported 14 more cases. The cholecystoduodenostomy is the most common form of an internal biliary fistula.

Cholecystoduodenostomy, whether spontaneous or operative is attended by the danger of an ascending cholangio-hepatitis. Consequently the operation is performed only as a palliative measure, when, for any reason, more extensive or definitive surgery cannot be done. Also, because of this danger, prompt surgical repair of spontaneous fistulae is generally urged.

Surprisingly little has appeared in the literature regarding the true incidence and severity of cholangio-hepatitis following cholecystoduodenostomy, either spontaneous or operative. Pomeranz et al (3) in reporting such a case remarked that at postmortem "microscopic study of the liver revealed no evidence of cirrhosis," although the duration of the symptoms in the patient was approximately five years. Gray and Sharpe (4) state, "The danger of ascending infection, recurrent cholangitis and hepatitis in which spontaneous internal biliary fistula is not treated surgically has probably been exaggerated, for the most common type of internal biliary fistula involves the gall bladder, and direct communication with the biliary tree is interrupted through the tortuous cystic duct and valves of Heister." However, in the cases of cholecystocolostomy, the second most common form of spontaneous fistula involving the gall bladder, hepatitis, cholangitis or both is much more prevalent. This seems to indicate that the prevalent bacterial flora plays an important role in the development of an ascending infection.

The following case is presented, not because of the rarity of spontaneous cholecystoduodenostomy, but because from clinical evidence the long duration of the lesion is known, and careful studies of liver function indicate but very mild liver dysfunction. No liver biopsy was done because the patient refused hospitalization and no liver biopsies are performed in the outpatient department.

CASE REPORT

J. D'A., Boston City Hospital OPD No. 682853, a 63 year old white widow was referred to the GI Clinic on 5-9-50 because of epigastric distress.

She had been well until *10 years prior to entry* at which time she was awakened at night with very severe epigastric pain, apparently colicky in character. Her physician administered morphia subcue and told her she had a gallbladder attack and should have an operation. No x-rays were taken. On bed rest and low fat diet the symptoms subsided after 1 or 2 weeks. The patient was told to avoid greasy and fatty foods. There was no known jaundice, dark urine, clay colored stools, hematemesis or melena. She improved on a medical regimen, and therefore refused operation.

Since then she had epigastric discomfort, bloating, belching, usually related to dietary indiscretion. In the ten-year period she had had 3 or 4 episodes of severe epigastric pain, flatulence and belching, the attacks lasting 2 or 3 days each. There was no history of jaundice, clay colored stools, or dark urine with these episodes. The last such episode was in September, 1949, for which the patient was seen at another hospital. In the year prior to entry she had lost an estimated 20 pounds. She denied chills or fever. She remained at work at a machine in a factory between the attacks, and was relatively asymptomatic except for intolerance to fried, greasy, and fatty foods. With dietary indiscretion she had episodes of upper abdominal discomfort, and a sensation of "gas boiling on the stomach." She was given "green pills" (presumably belladonna) and felt that these gave considerable relief of her symptoms. Bowels were regular. No history of ethanol, no known exposure to hepatotoxins.

P. H. Patient was born in Italy, had severe laryngitis 40 years ago, tonsillitis 35 years ago; and a 'thyroid operation' 26 years ago.

F. H. Non-contributory.

P. E. Obese WF of about stated age; no jaundice. Lungs clear. Heart normal sinus rhythm, no murmurs. Rate 60.

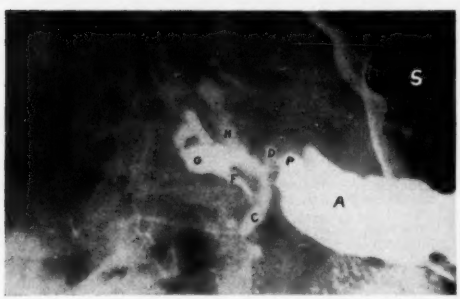

Illustration 1: Showing barium given by mouth entering the gall bladder and extrahepatic and intrahepatic ducts. S. is stomach containing air. A.—antrum. P.—pylorus. D—duodenal cap. C.—common bile duct. F.—fistulous tract. G.—gall bladder. H.—hepatic bile duct. I.—intrahepatic ducts.

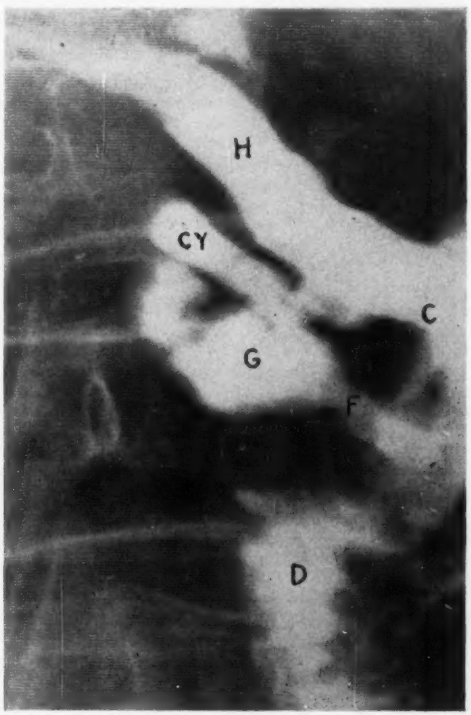

Illustration 2: A representative film of the second x-ray examination. C.—common bile duct. F.—fistulous tract. D.—2nd portion of duodenum. G.—gall bladder. Cy.—cystic duct H.—hepatic bile duct.

Abdomen obese. Liver, spleen, kidneys not felt. There was tenderness in the mid-epigastrium. Otherwise physical examination was within normal limits.

1st. G. I. Series (5-24-50) No. 96574 "Esophagus normal in size, contour, and tone. The barium passed readily into the stomach which was normal in size, shape and position with normal mucosal pattern and peristalsis. The barium passed readily into the duodenal bulb which appeared contracted and irregular in contour. The barium was noted to pass from the duodenal bulb into what appeared to be a shrunken, contracted gall bladder, thence via the cystic duct, the barium passed into the common duct and biliary radicles which were almost completely filled. The duodenal loop showed normal curvature, tone and mucosal pattern. The stomach showed normal emptying.

IMPRESSION: Cholecystoduodenostomy, probably on inflammatory basis; deformed duodenal bulb probably from old inflammatory scarring. Suggest re-examination for better evaluation.

2nd. G. I. Series (6-21-50) No. 96989 "Esophagus showed normal size, contour and tone. The barium passed readily into the stomach which was normal in size, contour and tone, with normal mucosal pattern and peristalsis. Barium passed readily into the duodenal bulb and then into what appeared to be a contracted gallbladder; thence via the cystic duct, the barium entered the common duct and biliary radicles. The duodenal loop showed normal curvature, tone and mucosal pattern. The stomach showed normal emptying.

IMPRESSION: Cholecystoduodenostomy, on the basis of chronic inflammation and scarring. Deformed duodenal bulb probably from old inflammatory scarring.

Liver Function Tests 6-30-50

BSP (5 mg. per kilo, 45 min. specimen)	16% retention
Cephalin Cholesterol Flocculation	1 plus in 24 hrs.
	2 plus in 48 hrs.
Zinc turbidity	4.6 (normal 2.4)
Zinc flocculation	3 plus.
Thymol turbidity	3.89 cc Barium Sulfate
	OR 11.7 McLagren units
Serum bilirubin	0.04 indirect
	0.4 total.

Repeat Liver Function Tests 2-26-51

Cephalin Cholesterol Flocculation		+
		−
Zinc Flocculation		+
		−
Thymol turbidity		7.03
Alkaline Phosphatase		5.12
Bilirubin	indirect	0.44
	Total	1.01

DISCUSSION

It seems very likely from the history that the severe episode ten years before study represented an acute gall stone colic with development of a spontaneous cholecystoduodenostomy. Unfortunately this point cannot be established with certainty. However, all her subsequent attacks were distinctly milder, of shorter duration and did not require opiates. The patient was asymptomatic prior to the first attack and following this developed intolerance to fried and fatty foods, with separate episodes of more severe upper abdominal distress. The G. I. Series showed an unequivocal fistula. Liver function in spite of the apparent duration of the fistula, was not markedly deranged, in fact on a repeat examination showed an improvement.

This case presents clinical evidence to support the previously noted contention of Gray and Sharpe (4) that the danger of an ascending cholangio-hepatitis in cases of spontaneous cholecystoduodenostomy may be exaggerated. However, in this case barium passed through the gall bladder and outlined not only the hepatic and common bile ducts, but also some finer biliary radicles within the right lobe of the liver. This indicates that the cystic duct and the valves of Heister are not always sufficient to prevent regurgitation of barium, chyme or food into the hepatic radicles. Even in the presence of such regurgitation a cholangio-hepatitis need not develop, despite a fistula that apparently persisted for 10 years.

Clinically a spontaneous fistulous tract may be suspected if large gall stones are passed in the stools, if they are vomited or cause an intestinal obstruction.

The diagnosis of a spontaneous cholecystoduodenostomy is dependent on x-ray visualization of air within the gall bladder and liver radicles (in this case absent) or more dramatically if barium given by mouth fills the gall bladder, extra-hepatic and at times intra-hepatic ducts as demonstrated on the attached films.

Despite this experience we do not advocate a watchful waiting attitude in spontaneous cholecysto-duodenostomy because infection of the biliary tract and liver parenchyma is an ever present danger. Surgical repair is the procedure of choice. In this case the patient persistently refused the proferred operation. A spontaneous cholecystoduodenostomy may close spontaneously with restoration of normal flow of bile. However, one is not justified to treat such cases expectantly when a relatively simple operation will cure the condition and eliminate the danger of a secondary cholangio-hepatitis. This becomes imperative if repeated liver function tests indicate increasing liver dysfunction and when liver biopsies demonstrate histologic changes in the liver.

CONCLUSIONS

A case of spontaneous cholecystoduodenostomy of 10 years duration without evidence of an infection of the biliary tract and with nearly normal liver function is reported.

A definitive diagnosis can be made by x-rays only, when either free air is seen in the biliary radicles or when barium fills the gall bladder, extra-hepatic and intra-hepatic bile ducts.

The treatment of choice is surgical repair of the fistula. Watchful waiting for spontaneous closure, which occurs rarely, is dangerous lest an infection with an ascending cholangio-hepatitis develop.

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PAST AND PRESENT CONCEPTS OF ENERGY METABOLISM AND OBESITY

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IN THE LAST 75 years, the philosophy of science has undergone a fundamental metamorphosis. The 19th century concepts of simple and pure causality, of ascertainable certainty, and dogmatic positivism, are giving way to an understanding of complex and multiple interrelationships, of the appreciation of the statistical approach and of Heisenberg's uncertainty principle, and to an awareness of the common presence of unsuspected but often critically influential variables.

Few subjects have lagged further behind in their development along these guiding lines of modern mathematics and physics than the problems of energy metabolism in clinical medicine.

The current approach is based on three fundamental propositions:

1. that the metabolic activities of the human organism can be equated with the mathematical concept of the thermodynamic heat engine;

2. that the basic metabolic processes can, in the last analysis, be summed up in unalterable equations of the form:

$$\text{glucose} \rightarrow H_2O + CO_2 + \text{energy (a fixed amount)}$$

and that consequently, measurement of gas exchange and total body calorimetry are sufficient to reveal the innermost secrets of physiological energy exchange;

3. and that the clinical problem of obesity is simply a matter of excess calories as expressed in the following quotation: "Fat comes only from food and obesity results only from eating more than is needed to meet energy requirements of the body" (Rynearson and Gastineau) (1).

The statement quoted above and other comparable utterances in the medical literature express the conviction that obesity is "caused" solely by the intake of food in excess of the requirements as calculated on the basis of oxygen consumption under "basal" conditions. Such remarks are usually followed by an offhand reference to the "laws of thermodynamics."

The widely held views about the "cause" of obesity are based on the impression that we are dealing with a simple situation. Yet on further consideration the situation is not quite as simple as it might seem. Let us assume, (and there is reason to do so), that a normal physiological process can be performed by the body with varying degress of efficiency. In the least efficient state, let the intake equal the "expenditure"; then, there is "balance". Should the process now proceed with maximum efficiency, less energy will be required and there will be less "expenditure," hence, positive balance or storage will ensue. In both instances the identical events take place, yet with a very different clinical result. Thus, it seems, that "expenditure" is a far more subtle concept than appears at first glance; its relationship to the equally involved concept of "intake" is of necessity far more complicated than the original proposition would lead us to believe.

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The rather off-hand reference to the laws of thermodynamics also deserves comment. While statements of this type lend superficial authoritativeness to the concept, they often reveal, in fact, an astonishing lack of familiarity with the various laws mentioned. One may even note, at times, a certain indecision as to which thermodynamic law is being called upon. Thermodynamic principles are, in fact, strictly limited mathematical concepts, and not vague philosophical generalizations such as might be expressed in the language of a high school physics textbook. To assume that heat measurements on the human body can be treated (mathematically) in a manner similar to the thermodynamic heat engine is naive to the point of fatuousness.

This opinion is shared by many prominent mathematicians and physicists; Norbert Wiener, for instance, has said: "In treating the human body from the point of view of entropy, you can never regard it as a heat engine, unless you modify your notion of temperature so as to obtain local temperature enormously higher than the measured temperature of the human body as a whole.

An alternative way of considering the living organism is to introduce chemical energies which at least partly pertain to reversible processes, and which bring the whole matter out of classical heat engine theory. In either case, our knowledge of the microscopic temperatures or of the chemical processes of the human body is not precise enough to introduce well measured notions of entropy; until the physiology of metabolism is considerably further advanced than now, the notion of entropy, while it is extremely useful as a philosophical background, does not represent a measurable quantity."*

Other physicists have gone further to point out that thermodynamic laws apply to "closed systems" in "dynamic equilibrium," whereas the human organism is more adequately treated mathematically as an "open system" in a "steady state,"—to which thermodynamic laws do not necessarily apply. And so it becomes increasingly evident that the seemingly unassailable, mathematically certain foundation of our clinical energy concepts is not so unassailable nor so certain, after all.

Among the older criteria used to measure metabolic events were, for instance, the dextrose/nitrogen ratio, oxygen consumption, respiratory quotient, and so on. Soskin has dealt exhaustively with the question of the D/N ratio and has shown that it is essentially without meaning (2). Evidence is also accumulating that the rate of O_2 consumption (usually measured for a matter of minutes and confidently extrapolated over a 24 hour period) is not an unequivocal index of the rate and trend of metabolic activity. For example, the transformation of ATP to ADP (release of a high energy phosphate bond) is the main source of energy in muscle tissue, yet there are no data linking the function of high energy phosphate bonds directly to

*Personal communication.

respiratory oxygen consumption. Many reactions within the body are known to proceed either by aerobic or non-aerobic pathways. Clinically, testosterone is known to cause an increase in oxygen consumption coincident with weight gain, and other evidence of anabolic activity.

For a long time the RQ was supposed to be an accurate index of the nature of bodily metabolic activity: a low RQ indicated predominant oxidation of fat while an RQ approaching the maximum (i. e., 1) indicated oxidation of carbohydrate. Unhappily for this theory, it has been amply demonstrated that foodstuffs are not simply burned, as fuel in a furnace, to carbon dioxide and water. Energy providing substances, be they carbohydrate, fat or protein, are broken down into small molecular fragments and merged into common pools such as the pyruvic acid pool, from which metabolic requirements for resynthesis as well as energy production are met. Furthermore, a number of unforeseen reactions have been discovered and observed, for example, the direct conversion of glucose into fat, a reaction which may utilize fully a third of a given dose of glucose, and which has an RQ of 8. It appears, then, that the RQ, as usually determined, is simply an average of the RQs of a vast number of largely unknown reactions, and is consequently (except in rigidly defined experimental systems) of little fundamental value (2, 3).

The opinion of the physicist about the interpretation of these physiologic data can be gathered from the following quotation: "Indeed, at the present time, one is able, by reactions known to occur, to account for the disposition of only a small fraction of the energy liberated in the complete oxidation of glucose to carbon dioxide and water" (Stetten, 4).

Isotope studies have opened new vistas in the investigation of energy metabolism. The rapidity of movement and interchange of individual atoms and molecular fragments is truly astounding. For example, at least fifteen percent of the sulfur atoms in the glutathione of the body are interchanged with "new" sulfur atoms within eight hours. By labelling certain molecules of the living protoplasm with isotopes it could be shown that after nine days, one-half of the molecules initially present are replaced by newly synthesized molecules (Stetten, 5).

Since the rapid turnover in living protoplasm has been demonstrated by Schonheimer and his associates, it was quite evident that atomic interchange within the molecule or turnover of molecular fragments within the living protoplasm requires energy: if the turnover is faster, more energy is required; if the rate diminishes, less energy is needed. Thus, there is a tremendous field for the conservation or expenditure of energy within the intermediate metabolism, not necessarily measurable in terms of heat production or respiratory gas exchange. Atomic or molecular exchange, furthermore, has its own energy considerations of a type unknown at the time of the development of classical thermodynamics.

The factors which determine the rate of turnover are poorly understood, although there is no doubt that hormonal influences are of great importance. Thus, it has been shown that the rate of synthesis of fatty acids in the diabetic animal is down to five percent of the normal. Administration of insulin, however, increases the rate of synthesis to four hundred percent above normal (Stetten, 5). Turnover rates are very low during starvation, and are known also to decline progressively with age. There is evidence that increased rates occur during overfeeding following prior starvation.

There are also other methods by which the organism can govern energy consumption, and thus influence the balance between intake and expenditure. Recent work on 32 individuals kept on a semi-starvation diet for six months has revealed important evidence that the body can adjust itself to reduced food intake by reduction in energy expenditure (Taylor and Keys, 6). Thus, the energy cost of activity at the end of starvation was *calculated* at 1200 calories for the reduced body weight. The *actual* cost of activity at that time, however, was found to be only 499 calories. The BMR was reduced to 31.2% of which 65% could be ascribed to shrinkage of the metabolizing mass of tissue; the remaining 35%, however, was due to a decrease in the intensity of metabolism. With the help of these and other adjustments the body weight became stabilized at a level of 75% of the original weight, though the caloric intake remained reduced to 45% of the pre-experimental food supply.

Other methods of the body to reduce energy expenditure include: variable efficiency in work performance, variation in the specific dynamic action of proteins, in the heat loss from the body surface, etc. These factors, significant in the energy economy, have been discussed in detail in previous publications (7).

Ingle has drawn attention to certain experiments which provide another fundamental insight into the problem of obesity and which are little known to contemporary clinical investigators. By five years of selective inbreeding of the offspring of a single pair of rats, Morris, Palmer and Kennedy were able to produce two strains having consistent differences in regard to the efficiency of food utilization. By efficiency of food utilization is meant the ratio between the amount of food consumed and the resultant weight gain. Despite the fact that there were no differences in ability to digest or metabolize food, involuntary activity or basal metabolic rate, the "high efficiency" strain stored (as fat) a much greater percentage of the ingested calories. Perhaps the basic mechanism of calorie conservations is, as Cannon suggests, a lesser energy requirement for the synthesis of new tissue in the "high efficiency" strain.

An important endocrine influence, hypothyroidism, has recently been studied by Scow. If animals are force-fed a diet which causes them to gain weight, they will accumulate fat and protein in a ratio of 1:2. If, however, the animals are first thyroidectomized, they will accumulate fat and protein in a ratio of 5½:1. Even in animals eating ad libitum, thyroidectomy changes the fat-to-protein ratio from 1:1.5 to 2:1. Similar abnormalities of the fat-protein ratio are also found in experiments where there is a deficiency of pituitary growth hormone. It may be that the changes observed in these thyroidectomized animals are mediated by the pituitary. At any rate, the endocrine system is extremely important in determining what becomes of calories once they are ingested; by the same token it is likely to influence the proportion of calories available for immediate energy requirements versus those which are stored in more or less accessible form.

The discussion so far has been primarily theoretical

in nature; there are immediately practical clinical aspects as well. Partly as a consequence of the delay in development of physical concepts of energy metabolism, it is a currently accepted view-point that any excess of body weight is merely an expression of overeating which, in the majority of instances, is the result of psychogenic factors. Contrary to this view, there is substantial evidence available that a variety of factors other than environmental stimuli, (e. g., emotional problems), such as lesions of the hypothalamus, etc., are capable of upsetting the normal mechanism which balances the desire for food (energy intake) against actual energy requirements. This normal balance can be upset by a great variety of forces acting at different points of this complex dynamic equilibrium. It is unfortunate that the direct and obvious simplicity of the overeating factor has distracted attention from more subtle but equally important aspects of the problem. Some of the known facts, influences and methods of approach deserve further discussion:

1. The word, "weight" or "overweight" is not synonymous with "fat deposit." Retention of sodium and/or water has been demonstrated repeatedly to be an important factor in obesity, but one which is completely outside the range of energy calculations or thermodynamic principles. Moreover, nothing is known of the normality of the metabolic reactions which are forced to proceed in a water-logged, electrolytically unbalanced protoplasm. The bloating, edema and weight gain of chronic starvation is another outstanding example of a non-coincidence of the terms, "weight" and "fat."

2. Fat tissue is all too often assumed to be an entirely passive "storage tank" with no other function than to act as an inert container. Quite to the contrary, Wells (8) and others have shown that the subcutaneous fat tissue is an organ with a definite function of its own and a considerable degree of autonomy. Functional activity of the fat tissue is shown by the fact that it can pick up glucose from the blood and convert it into fat; it may release this fat for utilization by other tissues or retain it, independent of the want or metabolic activity of the body (9). Not every part of the fat tissue possesses the same degree of autonomy, nor is it identical in different individuals. In some morphologically distinct types of fat tissue (such as brown or glandular fat of certain species), autonomy is far reaching and much greater than in ordinary fat tissue.

In man, local autonomy is also recognizable: fat tissue does not diminish appreciably in certain parts of the body even in extreme emaciation; for example, the buccal fat pads are still preserved in emaciated, marantic infants. The trochanteric fat pads of hypogonad women resist weight reduction by dietary or any other means. The abdominal fat pad of elderly males is equally resistant. The use of abdominal skin and subcutaneous fat tissue in plastic repair of other parts of the body has resulted in the development of unsightly accumulation of fat coincident to accumulation of fat in the abdominal wall. The uneven fat distribution peculiar to certain types of obesity and associated in the older literature with certain endocrinopathies also shows relative resistance to weight reduction by dietary means although the simultaneous weight loss of other parts of the body may be conspicuous. Such fat pads are more likely to recede with the therapeutic use of the ketogenic factor of the anterior pituitary (11). In lipodystrophy the massive accumulation of fat over the lower half of the body is often associated with extreme emaciation of the upper half. Whatever the caloric balance might be in such patients, it cannot explain the divergent manifestations occurring simultaneously in different parts of the body.

3. The influence of hormones and endocrine glands on the accumulation and mobilization of fat is well established. Most of the pertinent literature has been summarized in previous publications (*7*). It is established that utilization of ingested carbohydrate, gluconeogenesis, nitrogen balance, and deposition or mobilization of fat are all to a large extent under hormonal control. Most enlightening (and altogether incompatible with the current belief that fat deposits are governed solely by the caloric intake) are observations on adrenalectomized animals; they lose more weight than the pair-fed, unoperated controls and gain weight more rapidly than the controls upon administration of cortical extract. Equally significant is the fact that the ketogenic factor of the pituitary (which is probably identical with the growth hormone) mobilizes the depot fat in the presence of adrenal cortical steroids. The ketonuria observed after the injection of pituitary extract is thus, in a sense, comparable to the ketonuria following the intake of a substantial fat meal. Patients with uneven fat distribution of the "hypopituitary" pattern, as might be predicted, show no ketonuria after the ingestion of fat (12).

4. Patients observed on a regulated 800 calorie diet have failed to show weight loss although determination of the BMR indicated a higher caloric "requirement." Weight loss was slow and below expectation even when the intake was reduced to 450 to 500 calories. The factor of disturbed water balance was carefully eliminated. Yet, adequate weight loss could be induced at the 1000 to 1200 caloric intake level with appropriate supplemental endocrine medication.

5. Lastly, and perhaps most important of all, one must bear in mind that obesity is, after all, only a symptom and as with all other symptoms, it is undoubtedly the result of variable single or combined causative forces. Analysis of such a heterogeneous group of cases, alike only in respect to obesity, may be expected to obscure rather than reveal the sought-for abnormalities by yielding "average" values similar to those of other heterogeneous (e. g. "normal") groups. Thus metabolic studies of many obese people show perfectly "normal" findings; in other cases of obesity, however, varied metabolic abnormalities are noted. Such deviations from the normal are particularly common in individuals who show abnormal fat distribution and who often present highly suggestive evidence of an endocrine disturbance.

Statistically significant differences relating to the BMR, SDA of proteins, glucose tolerance, blood uric acid, lymphocyte and eosinophile counts, and the ability to excrete a test dose of sodium and water, can and have been demonstrated, provided the investigated obese individuals are grouped according to certain well-defined criteria (10).

CONCLUSION

It is essential to realize that the contemporary clinical concepts of metabolism are due for a thorough and

fundamental revision; that the problem of obesity must be considered as the question of a symptom and not of a disease; and finally, that our increased knowledge of the complex hormonal-metabolic relationships contradicts the assumption that in obesity a single, all-important causal factor operates uniformly upon the individual members of a quite heterogeneous group of human beings.

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SERUM AMYLASE IN PEPTIC ULCER*

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THE USE OF serum amylase determinations in the diagnosis of acute pancreatitis is well known. The question has been raised, however, as to what the serum amylase levels may be in other gastrointestinal disturbances with clinical symptoms resembling those of acute pancreatitis. Wapshaw in 1949 (1) reported serum amylase values in 30 cases of perforating peptic ulcer and Probstein, Wheeler, and Gray in 1939 (2) reported on 17 such cases. In 3 cases the amylase levels were high enough (above 600) to cause erroneous diagnosis of acute pancreatitis. In both of these investigations, Somogyi's (3) method for serum amylase determinations was used. There are a few earlier reports on serum amylase levels in peptic ulcer cases but the methods used were different and in most cases ones whose accuracy has since been questioned. We have investigated serum amylase values in 19 random cases of peptic ulcers using a modification of the Somogyi method and wish to compare our findings with the two previous reports.

PATIENTS

The subjects in these experiments were patients in the gastro-intestinal clinic or the medical and surgical wards of the Louisville General Hospital. In fifteen cases, the diagnosis of peptic ulcer was confirmed by x-ray findings and in the other four, the presumptive diagnosis was peptic ulcer because of hematemesis and other symptoms but the x-ray findings were doubtful. Of the 15 with a confirmed diagnosis of peptic ulcer, 13 had duodenal ulcers, a stomal ulcer, and one a gastric ulcer. All ulcers were active but only two were penetrating at the time blood was drawn for analysis.

ANALYTIC METHODS AND RESULTS

The method for serum amylase determinations was a modification of Somogyi's (3) method. The reduced copper (and thus the reducing carbohydrates) was measured by the Folin-Wu method (4) in place of the iodometric method given in Somogyi's original procedure. A Model II Universal spectrophotometer was used. Results are summarized in Table I.

TABLE I

SERUM AMYLASE LEVELS IN CASES OF PEPTIC ULCER

Patient	Serum Amylase in Somogyi Units	Diagnosis	Remarks
1.	45	Duodenal Ulcer	
2.	154	Duodenal Ulcer	
3.	101	Duodenal Ulcer	
4.	94	Duodenal Ulcer	
5.	126	Duodenal Ulcer	
6.	93	Duodenal Ulcer	
7.	200	Duodenal Ulcer	Penetration into liver
8.	65	Duodenal Ulcer	Penetrating
9.	45	Duodenal Ulcer	
10.	104	Duodenal Ulcer	Penetrating
11.	233	Duodenal Ulcer	Long Ulcer History
12.	132	Duodenal Ulcer	
13.	53	Duodenal Ulcer	
14.	124	Stomal Ulcer	
15.	40	Gastric Ulcer	
16.	112	Presumptive Peptic Ulcer	
17.	100	Presumptive Peptic Ulcer	
18.	134	Presumptive Peptic Ulcer	
19.	100	Presumptive Peptic Ulcer	

DISCUSSION

It was thought that when there is a lesion in the gastrointestinal tract with which pancreatic fluid may come into contact, there might be a possibility of the entrance of pancreatic enzymes into the blood and consequently a significant rise in their concentration. With active peptic ulcer there would also be the possibility of secondary inflammatory involvement of the pancreas with occlusion or partial occlusion of the duct causing back pressure which might result in increased absorption of pancreatic enzymes into

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the blood stream. Apparently, this was not the case here since in 17 of our 19 cases the serum amylase values were within the accepted normal limits of 80-180 Somogyi units or were subnormal. Of the two that showed amylase levels that were somewhat elevated above normal (patients 7 and 11), neither showed clinical evidence of pancreatic involvement. Patient 11 had a long history of chronic duodenal ulcer which was active and bleeding at the time of this experiment. Patient 7 had an ulcer that showed very deep penetration into the liver which is perhaps a little surprising since empirically it has been found that damage of the liver is associated with a subnormal amylase level (5).

These findings, even though mainly not on perforating ulcers, seem to agree with previous results (1, 2) where the serum amylase levels in cases of perforating peptic ulcers were for the most part normal or subnormal. In Wapshaw's study, only 6 out of 30 cases showed abnormal amylase levels and only 2 of these were sufficiently elevated that erroneous diagnoses of acute pancreatitis were made. In the 17 cases reported by Probstein, Wheeler, and Gray, only 4 showed high amylase levels and only one of these was high enough to prompt a diagnosis of acute pancreatitis. These data also seem to agree with the findings of Jergesen and Simonds (6) who reported no significant elevations in the levels of serum lipase in 50 patients with peptic ulcer. Although not reported, it is likely that the serum amylase levels of these patients would have been normal.

SUMMARY

In 15 proven and 4 presumptive cases of peptic ulcers, only 2 showed high amylase levels and these were not sufficiently elevated to be confused with those found in acute pancreatitis. These results agree in general with the previously reported cases where the serum amylase was measured by Somogyi's method.

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RUPTURE OF THE ESOPHAGUS INDUCED BY VOMITING*

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THE TERM "spontaneous rupture of the esophagus" often is employed to describe a laceration extending through the wall of the apparently normal esophagus without obvious cause although frequently there is antecedent vomiting or retching. In the ordinary case the contrast to traumatic rupture in which the esophagus is torn or crushed as the result of some extrinsic force is sharp. Sometimes, however, assignment of a given case to one category or the other is rather arbitrary. Thus, necropsy disclosed a scar near the laceration in a patient who ruptured his esophagus while defecating (Adams); the esophageal muscle may be atrophic (Krückenberg), syphilitic perivascular infiltration may surround smaller esophageal vessels (Glass and Freeman) or minute abscesses may be seen in the muscle (Williams and Boyd). Under such circumstances the esophagus may rupture during a convulsion or some similar act. At other times trauma is unmistakable but its exclusive responsibility questionable as exemplified by esophageal rupture in a healthy child who jumped off a wagon or in an adult who fell from a horse. Perforation of the esophagus during the natural evolution of some intrinsic disease (carcinoma of the esophagus), by the extension of some nearby process (erosion of an aortic aneurysm), or by superimposed trauma (instrumentation) in such cases is adequately described by unqualified terms like rupture or perforation.

Despite an overlapping nomenclature and the dubious reality of a purely "spontaneous" rupture, the concentration on spontaneity has some practical value since it emphasizes the existence of this accident in patients without known or suspected esophageal disease as the result of some trivial strain. Until recently this important fact has been neglected and many treatises on esophageal disease fail to mention it or merely state that spontaneous rupture is a pathological curiosity. Consequently the possibility does not enter into consideration in differential diagnosis although the brutal onset and fulminating evolution invariably stamp the situation as desperate. Often the surgeon undertakes fruitless abdominal exploration for a nonexistent perforated duodenal ulcer or the internist waits for further evidence on which to establish diagnosis of a myocardial infarction, dissecting aneurysm, or pulmonary embolism. Thereby precious time is lost in the face of a catastrophe which runs its course in a matter of hours. If some peculiar phenomenon like cervical subcutaneous emphysema happens to develop or huge quantities of fluid rapidly collect in one or both pleural cavities the distinctive clinical picture may be recognized belatedly by those who are aware that "spontaneous rupture" of the esophagus occurs. A correct preoperative diagnosis has been reached in only 14 cases and definitive surgical therapy has been tried only in 3. The survival of one operated patient for a week, death then resulting from pulmonary embolism, proves that repair is feasible and recovery is possible (Barrett). If ad-

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ditional evidence were needed to indicate the widespread unawareness of the existence of the accident, reference might be made to the fact that case reports seem limited to medical journals published in English, French, and German.

CASE REPORT

A 50-year-old colored male was admitted to Metropolitan Hospital shortly after midnight, January 1, 1951, because of chest pain and dyspnea of five hours duration.

He became ill while at work washing dishes in a restaurant. About 7:00 p.m. the evening of admission he had two loose bowel movements. Shortly thereafter, he experienced some epigastric uneasiness with a single episode of vomiting. The vomitus consisted of food eaten several hours earlier. Almost immediately after vomiting, he experienced very severe lower chest pain and shortness of breath.

The past history was entirely negative and alcoholism was denied.

On admission the patient was acutely ill, anxious, and so dyspneic that he insisted on sitting on the edge of the bed. The pulse was 140, respiration 50, and blood pressure 130 systolic and 90 diastolic. The temperature was 101°.

There was marked bulging in both supraclavicular regions suggesting subcutaneous empnysema. The trachea was markedly shifted to the right; some rales were audible in the right base. The electrocardiogram was negative apart from inverted T waves in leads 1 and V 5. X-ray examination disclosed deviation of the trachea to the right, clouding of both bases, somewhat more marked on the left, subcutaneous emphysema in the neck and in the anterior chest wall; a Bucky film of the chest also showed air behind the heart.

The dyspnea did not improve despite the administration of oxygen. The severe respiratory distress increased as dullness and rales developed in botn bases posteriorly. Further examination and treatment apart from penicillin were refused. Death occurred 28 hours after admission.

The postmortem findings of interest were limited to the chest. On removing the sternum a large number of air bubbles escaped and marked edema of the mediastinum was noted. The thoracic organs were displaced to the right by collection of fluid in the left pleural cavity which exceeded 2.5 liters in volume and consisted of a dark straw colored material containing some solid red particles. Displaced mediastinal structures compressed the right lung. The right pleural cavity was obliterated by old, very firm, widespread adhesions; similar adhesions existed in the upper left pleural cavity.

The larynx, trachea and bronchi were normal save for the presence of a viscid dark mucus. The lungs showed extensive consolidation and congestion and a dark red foamy fluid could be expressed from cut sufaces. The mediastinum was carefully opened and posteriorly a collection of dark fluid containing food particles was found. There was marked edema and necrosis of the connective tissue of the posterior mediastinum.

The lower third of the esophagus contained several distinctly soft areas. Three centimeters above the cardia, there were two lacerations in the left postero-lateral wall. Both of these perforations were located at the base of adjacent longitudinal folds in the mucous membrane. The larger of these perforations was a trifle over a centimeter in length and its center was about 1 cm above the level of the second perforation in the adjoining esophageal fold. The larger perforation is longitudinal in nature while the smaller has an almost circular erosion at the lower end of the slit. In addition there are three mucosal erosions, one proximal and two distal to the perforations; these erosions do not extend through the superficial layers of epithelium. In both lacerations all layers of esophagus are visible. No varicosities, leukoplakia or foreign bodies (see below) were found on careful examination.

No abnormalities were noted in the stomach or intestines.

Apart from the bilateral bronchopneumonia, the most interesting findings were noted in the esophagus. Several small abscesses were found in the muscularis and one of these is shown in Fig. 1. It was the distinct impression of all who reviewed the slides that these abscesses were at least 48 hours old and therefore probably antedated the rupture. Moreover, in the base of the ulcer reproduced there were several partly digested voluntary muscle fibres, not of esophageal origin and presumably represented food fragments. A few of these muscle fibers were partly encapsulated likewise suggesting that the lesion was somewhat older than the case history implied.

At the base of both perforations, the periesophageal tissue was necrotic and led to a plum-sized necrotic cavity which contained food particles as well as the dark material previously mentioned. This cavity had ruptured into the left pleural space; no connection between the right pleural cavity and the mediastinum was found.

The presence of well digested partly encapsulated voluntary muscle fibres in one necrotic area in addition to the age of other minute abscesses in the vicinity required a change of opinion that spontaneous rupture of the esophagus had occurred. It seems more likely that one or two days prior to the catastrophe some foreign body, perhaps impacted bolus of meat, had provoked an initial mucosal lesion and permitted the entrance of an infection. The actual perforation seems to have been released by the vomiting, particularly since the second laceration contained no food particles and no inflammatory changes.

COMMENT

The original description of spontaneous rupture of the esophagus by Boerhaave in 1724 was so complete that little was added to the symptomatology afterwards. Apart from infrequent case reports the accident attracted little attention until 1877 when R. H. Fitz critically reviewed the literature and added a new example. Although only 3 cases satisfied his criteria, the study received widespread attention and launched a series of investigations. His principal difficulty was the exclusion of gelatinous softening and rupture of the esophagus, a postmortem event originally studied by John Hunter in 1786. Emphasis upon this occurrence followed Carswell's suggestion in 1838, namely that regurgitated acid gastric contents might expedite or provoke esophageal dissolution after death. Actually isolated or predominant postmortem destruction of the esophagus is unusual and perforation for this reason is observed in less than one necropsy in 3000. This might be anticipated for gastric acidity often becomes very low or vanishes as an agonal event; moreover, as a rule, acid gastric contents speedily become anacid after death. An agonal esophagitis provoked by profound shock with poor circulation to account for embolism and thrombosis in the submucous tissues and muscles was known to occur in typhoid fever or other forms of sepsis. In the patients under discussion, however, shock is secondary rather than initiating and patients with spontaneous rupture are stricken while enjoying apparent health.

At all events, Zenker and v. Ziemmsen, attracted by the compilation of Fitz, revived the old conception of esophagomalacia which had been popularized by Rokitansky. To explain its antemortem occurrence, they added an idea of Andral, namely that during vomiting the pallor of the face might be reproduced in the gastrointestinal mucosa. This ischemia could act as a releasing factor since vomiting was often the initial event in spontaneous rupture. Moreover, as an antemortem process, the chemical-peptic digestion proceeded more rapidly since the reaction took place at body heat. The conception of esophagomalacia seemed necessary since, on the average, 8.5 kgm. had to be applied as traction to the freshly excised human esophagus, in order to rupture it. Subsequently their theory was modified to include unusually acid gastric juice, constitutional weakness or anomalous development of the esophagus and so forth.

These traction experiments were adversely criticized

by Mackenzie, Brosch and Bleicher on the basis that spontaneous rupture depended upon bursting of the muscle rather than traction. Each of these observers ligated the upper end of the excised esophagus and injected fluid into the lower end. The methods employed varied somewhat but they found, respectively, that the average pressures necessary to burst the esophagus were 2.5, 1.5, and 0.5-2.0 kgm per cm^2. Brosch also observed that exposure of the normal esophagus for several hours to gastric juice of cadavers did not appreciably change the bursting pressure although similar incubation with an esophagus, weakened for some reason, lowered his figure. Interest in bursting pressures rapidly waned, however, after Duval showed that with air-induced rupture, the speed with which air was introduced rather than the total pressure was the determining factor. The effective pressures in such experiments are well within the limits which might develop during vomiting and they should not be compared with the far greater pressures employed in hydrostatic dilatation for cardiospasm; in the latter the enveloping silk bag determines how widely the esophagus will be stretched while the dilator is in place.

The normal mucosa of the gastrointestinal tract is somewhat more resistant to tearing than the underlying muscle. For the esophagus the respective figures are 4 and 3.49 pounds (Burt). If excised normal intestine is inflated, the serosa tears first and then the muscle, so that in properly arranged experiments the intact mucosa bulges into the gap created by the lacerated muscle. Moreover, in some patients with spontaneous rupture, the mucosa seems normal save for the laceration, the edges of which show only a slight deposition of fibrin. As noted earlier, minimal lesions in the muscle are frequently observed in patients with spontaneous rupture of the esophagus. For these reasons many assume that when the esophagus ruptures the laceration begins in the muscle.

On the other hand linear erosions of the mucosa of the stomach and of the esophagus may extend down to the circular muscle in alcoholic subjects. As will be shown below most instances of spontaneous rupture have been reported in patients who were chronic alcoholics and so-called spontaneous rupture of the esophagus has been observed in individuals who had classical mucosal fissures of chronic alcoholism in both esophagus and stomach. Leukoplakia of the esophagus is not unusual in chronic alcoholism and might provide a weak point; such leukoplakia, if missed at necropsy, may at times be destroyed by the laceration. The rent in the mucosa usually is more extensive than the tear in the muscle. Reference should also be made to the difference in length of the rupture in spontaneous tears versus those occurring in connection with various diseases which have provoked a periesophagitis. In the latter, as a rule, the muscle tear is much shorter than in spontaneous rupture suggesting that scars support rather than weaken the muscle and prevent extensive tearing. Finally, careful microscopic studies of the mucosa and muscle usually have not been included in case reports of "spontaneous" rupture of the esophagus.

With three exceptions the laceration has been longitudinal in spontaneous rupture. A similar situation seems to prevail with allied lesions elsewhere in the gastrointestinal tract. Thus, the laceration is usually longitudinal when a prolapsed rectum ruptures during defecation. If the intestine is ruptured experimentally by inflation, the laceration is regularly longitudinal in orientation; this has a clinical counterpart in the lacerations of the bowel observed in shipyard workers during World War I when nozzles of compressed air lines were placed in or near the anus as a practical joke. Longitudinal tears occur along the lesser curvature of the stomach after a compressive abdominal injury provoked by kicking or blows. Oddly enough, in Boerhaave's original case the laceration was transverse; the same situation prevailed in the patient of Petren although the laceration of the esophagus was created by the force of air from a compressed air hose, the nozzle of which happened to be in the patient's mouth when pressure was released. The direction of the tear can be explained equally well by the longitudinal folds of the esophagus or some weakness in the outer coat of the tube. It is a well known but unexplained fact that lead pipes, when subjected to pressure from water, tend to rupture longitudinally. When two lacerations exist, as in the case above, ordinarily both are longitudinal.

Equally striking in spontaneous rupture is the limitation of the laceration to the juxta-diaphragmatic zone. Spontaneous rupture of the esophagus occurs only in the lower third of the esophagus. The case of Petren, just mentioned as an example of traumatic rupture following intraesophageal pressure equivalent to 7 atmospheres, the tear was located at a level just below the bifurcation of the trachea.

Usually the laceration is described as occurring 0.5-2.0 inches above the hiatus; if measurements are made from the cardia, the figures are, ordinarily, 2-4 cm above the cardia. Only one case (Charbonnel and Darmaillacq) in our notes contains a specific statement of subdiaphragmatic spontaneous rupture although it is not uncommon for suprahiatal mucosal tears to extend downward to involve the cardia. Although anatomists often state that the esophagus extends 4 cm below the hiatus, gastroscopists deny that this situation prevails in the living and some assert the cardia is immediately below the hiatus. Consequently it seems safe to assume that rupture occurs at or just above the hiatus in practically all cases.

Usually the lacerations are 3-4 cm. in length but they may be as short as 1 cm. or as long as 6 cm. The mucosal tear is regularly longer than the laceration in the muscle. Most tears are in the posterior one-half although anterior ones are by no means unknown. A vast majority of patients suffer from rupture along the left aspect of the esophagus and the susceptibility of the postero-sinistrad face of the tube accounts for the frequency with which rupture ultimately occurs into the left pleural cavity.

No explanation advanced for the site of the rupture is completely satisfactory. The assumption that fixation of the esophagus to the diaphragm explains the level lacks an anatomic basis since the connections are very loose. Moreover, at the cardia the muscle tends to be reinforced by fibers from the stomach. The infrequency of esophageal rupture in children has been attributed to stronger and relatively thicker muscle in young individuals; certainly the muscle tears less rapidly from traction. Both idiopathic hypertrophy of the muscle at the cardia as well as achalasia have been suggested without supporting evidence. The portion of the esophagus which tears is composed almost entirely of involuntary muscle in contradistinction to the rest of the

tube but the possible etiological significance of this fact does not seem to have attracted much attention. Moreover it has been claimed that the more intimate relation of the right pleura to the esophagus provides support which is absent on the left side but the tissues are not in approximation and either fixation or support from this source seems rather improbable. Actually the esophagus readily undergoes displacement to right or left in a variety of mediastinal diseases without awakening the impression of restricted movement by tissue fixation. The slope of the esophagus from right to left within the thorax is so gentle that it would appear doubtful that this curve could be an effective factor. Finally intrinsic defects of the muscle of a congenital origin have been suspected, presumably on the basis that such anomalies have a counterpart in spontaneous neonatal rupture of the stomach; actual defects in the esophagus have, however, not been reported in patients with spontaneous rupture

Explanations taking their point of departure from a lesion in the mucosa rather than the muscle have also been offered. A relationship between spontaneous rupture and esophageal ulcer has been advocated ever since Quincke noted these ulcers in 1879 and Fraenkel (1899) reported the presence of heterotopic gastric mucosa in the esophagus. Since such islands occur principally in the upper esophagus while ulceration is found chiefly in the lower third, it was necessary to add the assumption that acid secretion ran down the esophagus, collected just above the cardia, and provoked ulceration. The trend of subsequent investigations points unmistakably to the fact that these glands secrete mucus and not hydrochloric acid and it seems unnecessary to invoke aberrant gastric mucosa in the esophagus as a cause of ulceration and rupture. Moreover, these ulcers occur in an older age group than the average example of spontaneous rupture, are characterized by hemorrhage (53%) rather than perforation (14%) at the onset, and have been usually missed in so-called spontaneous rupture. Peptic ulcer of the esophagus in a vast majority of cases is solitary and does not show multiple lesions as did the case under discussion.

Cushing observed esophageal ulceration in conjunction with certain brain tumors and esophageal perforation has been recorded in patients with a compound fracture of the skull, in tuberculous meningitis, and in cerebral syphilis. The patient who also had a skull fracture was a man who had been "more or less drunk every day for twenty years"; the patient with tuberculous meningitis had severe vomiting and those with cerebral syphilis ruptured the esophagus during epileptiform convulsions. It appears unnecessary to invoke an intracranial factor in the etiology of spontaneous rupture of the esophagus.

Three patients who died from a ruptured esophageal ulcer also had old duodenal ulcers (Hertzog and Leighton). Tilleston noted pyloric or duodenal stenosis in 23% of his 40 patients with esophageal ulceration. Vinson encountered 9 cases of esophageal stricture among 40 patients who had pernicious vomiting of pregnancy. Stricture of the esophagus is reputed to be a not unusual complication of duodenal ulcer (Larson, Layne, and Howard) although a relationship has not been noted by the present writers. At all events the development of an esophagitis as the result of repeated bouts of vomiting with consequent erosion, ulceration or some other lesion of the mucosa may play a more important role in some patients with esophageal rupture than has been suspected. The case histories just mentioned indicate that the past history of patients with esophageal rupture may indicate the presence of old duodenal or gastric (Petren) ulcer; in short, many patients have not been entirely well and, when the catastrophe develops, a positive history may prove very misleading.

Spontaneous rupture of the esophagus occurs primarily in males. Thus 22 of 24 consecutive patients were of this sex; there is a similar although less striking dominance of males (5 males: 1 female) in traumatic esophageal rupture but this seems to depend upon greater exposure to injury.

Twenty-five of 35 patients with spontaneous esophageal rupture were between 30 and 60 years of age and the average age is close to 42 years. Only 3 instances of spontaneous rupture have been reported in children

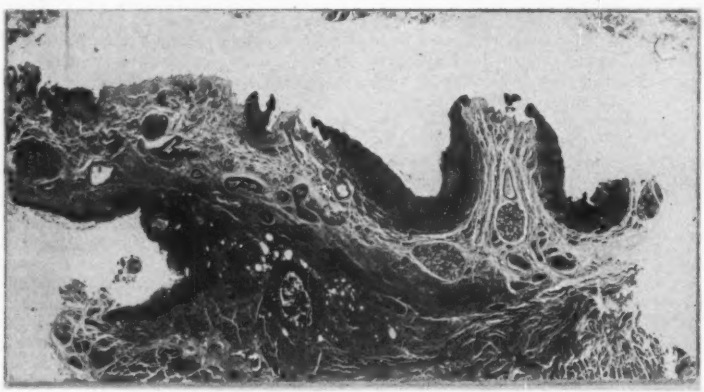

Fig. 1: Microscopic section showing at the right the largest abscess in which partly encapsulated voluntary muscle fibers (ingested meat?) were found. This abscess led to a plum-sized cavity in the mediastinum which contained air, fluid and digested food particles. The mediastinal cavity had ruptured into the left pleural cavity.

and not all of them are clear examples of "spontaneous rupture;" on the other hand rupture often occurs in children with esophageal ulcer associated with repeated vomiting, prolonged difficulty in eating, and debilitation. The age group with spontaneous rupture is definitely younger than those with peptic ulcer of the esophagus for 90% of the latter are over 50 years of age. Moreover the disparity in the two sexes is not as marked with esophageal ulcer in which the ratio is about 28 males to 12 females.

As indicated earlier, a large number of those who sustain spontaneous rupture of the esophagus indulge in alcohol to excess. Among the first 19 cases reported, 11 were alcoholics, 4 were abstainers, and the social habits of 4 were unknown. A definite history of alcoholism was obtained in 18 of 30 consecutive cases. In several other instances the individual drank considerable quantities of beer or wine just prior to the accident. Apparently alcohol may play a role by the production of esophageal erosions, by provoking vomiting, or by providing the fluid to be vomited.

Another rather regular feature is the occurrence of spontaneous rupture of the esophagus in voracious eaters; some patients have been veritable gluttons. Boerhaave's patient was notorious in this respect and was in the habit of inducing vomiting by titillating his uvula or taking emetics after overeating; he ruptured the esophagus after a bout of eating and drinking in which he had attempted to induce vomiting by both methods. In several instances the esophagus has been ruptured in an attempt to dislodge a real or fancied bolus of impacted meat. Actually it is rather unusual to miss violent vomiting at the onset. Vomiting was the first symptom in 23 of 35 patients. In 4 it was induced to dislodge impacted food and many others drank salt water, milk, or took an emetic shortly before. The term violent is employed to characterize the forcible nature of the emesis rather than recurrence of the episode; in fact the transient nature of the actual vomiting, often only a single attempt, contrasts strongly with recurrent vomiting and retching after the stomach has been emptied in other syndromes which might come under diagnostic consideration, in acute hemorrhagic pancreatitis of alcoholics for example. In a small number of patients retching rather than vomiting preceded the rupture and once or twice cough was the initial symptom; usually cough does not occur until intrapleural rupture takes place.

As previously implied vomiting occurs shortly after the ingestion of an unusually heavy meal. In this respect it resembles traumatic laceration in which the esophagus is lacerated much more easily if the compressive abdominal injury is inflicted shortly after eating.

While it appears inaccurate to designate a single releasing factor, in a vast majority of cases the sudden violent ejection of a large amount of food and liquid is the immediate precipitating cause. Probably the location of the laceration near the hiatus is connected in some way with a failure or inability of the muscle in this area to relax at the proper moment, although the susceptibility of this area to local alterations is notorious. This suggestion finds some support in the fact that rupture still tends to occur near the hiatus when lacerations are produced by vomiting in a patient with a benign stricture high in the esophagus; under these circumstances rupture often occurs far below the site of the stricture. If constriction of the muscle plays a role, presumably the laceration does not start in a healthy mucosa for contraction of the muscle tends to create additional mucosal folds rather than render it taut.

The vomitus often is described as coffee ground in appearance and usually contains food, alcohol and, at times, some blood. It is uncommon, however, for the appearance to be dictated by the presence of digested blood and the absence of profuse bleeding also contrasts strongly with the onset of symptoms in esophageal ulceration. In one patient who had bloody vomitus, symptoms had been present for 6 months and the spontaneous nature of her ultimate rupture might be questioned (Foggitt); in another it may have been produced by a coexistent gastric ulcer (Petren). There was, however, another patient with bloody vomitus who ruptured the esophagus while lifting (Griffith).

Agonizing pain is experienced during or immediately after the emesis. In 4 patients (Wolff, Griffin, Harrison, Lindeman), there is the report of feeling or hearing something tear. The excruciating pain is constant and usually fails to respond to morphine; often the patient cannot lie down or remain quiet. The site of the distress is low substernal or high epigastric or in the lower left chest; frequently it seems too high for an abdominal lesion and too low for a thoracic accident. Radiation of the pain to the back or interscapular area is common. Thirst may be severe and dysphagia absent; in a few patients however the pain was aggravated by swallowing as well as by deep breathing.

The pale anxious individual is bathed in a cold sweat and soon develops shock. Cyanosis appears somewhat later. Often the patient attempts to maintain a semi-sitting position with the body inclined somewhat forward and supports himself with both hands. The pulse is rapid; respirations are also fast and labored so that dyspnea becomes a major problem. Blood pressure tends to fall as shock progresses. The temperature usually is slightly subnormal but need not be altered.

Frequently the upper abdomen is rigid while it is soft below the navel. Rebound tenderness is very unusual and often no abdominal tenderness develops at all.

Early, the chest is not remarkable. After the lapse of a few hours signs of a tension pneumothorax may appear but more often fluid and air rapidly collect in the left pleural cavity. The appearance of a huge collection of fluid and air in this cavity is so noticeable that most patients are subjected to paracentesis which permits the recovery of fluid containing food and often alcohol. The discovery of gastric contents in fluid obtained from a pleural cavity by paracentesis clinches the diagnosis if gastric herniation into the thorax can be excluded. If the patient survives for a day, fluid may also collect in the right hemithorax although the character of the fluid in this pleural cavity suggests an acute inflammatory process rather than a ruptured viscus; in rare instances, rupture may take place on the right instead of the left or into both. With increasing pressure in the left pleural space, the mediastinum is displaced to the right, usually of sufficient extent to cause tracheal deviation to that side.

Subcutaneous emphysema in the neck appears after a lapse of a few hours in most patients. Thus it was

present in 16, absent in 3, and unmentioned in 12 of 31 early reports; it was noted in 17 of 24 more recently reported patients. Usually the emphysema remains limited to the neck and chest although in one patient it extended to the crest of the ilium. Since a search is regularly made for air beneath the diaphragm when rupture of a viscus is suspected it seems advisable also to obtain antero-posterior and lateral films of the chest. Presumably the diagnosis of ruptured esophagus would be made earlier in a larger percentage of patients if this became a routine procedure under these conditions. At first the mediastinal emphysema is localized but later it becomes extensive so that the film should be repeated after an hour if the first view does not provide the diagnosis. Films may disclose emphysema of the mediastinum and soft tissues and later the collection of fluid and air in one or both pleural cavities. All but 7 of the reported patients had a hydropneumothorax. In a few patients the diagnosis has been confirmed by the oral administration of a few mouthfuls of barium sulfate or lipoidal and the passage of the material into the pleural cavity. From a practical standpoint, the employment of contrast media is merely confirmatory and usually will be found unnecessary.

In the past spontaneous rupture of the esophagus soon ended fatally in practically every instance. The duration of life as a rule is less than 24 hours. Thirteen patients died in less than 12 hours, 24 in 12-24 hours, 8 in 24-48 hours and only 8 lived longer; one died after 9 days and another after 17 days.

SUMMARY

Although symptoms referable to the alimentary tract were present in 17 of 23 consecutive patients prior to "spontaneous" rupture and microscopic lesions were found in the esophageal muscle in many other patients, the fiction of spontaneity has practical value in emphasizing the occurrence of this fatal catastrophe after slight exertion in the absence of known esophageal disease.

Most of the patients are between 30 and 60 years old and the average is near 42. The accident occurs principally in males and usually is initiated by natural or induced vomiting shortly after excessive eating and drinking.

The laceration begins near the level of the diaphragmatic hiatus and extends longitudinally for 3-4 cm through all layers of the esophagus to enter the mediastinum, as a rule, along the postero-sinistrad aspect of the esophagus and hence into the left pleural cavity. Occasionally two lacerations are present and rarely rupture occurs in the right pleural cavity; both cavities may be involved simultaneously or by extension.

The mucosal tear is regularly longer than the muscle laceration and often a small ulcer is found at the lower end of the tear. Many observers are inclined, on the basis of experimental as well as microscopical evidence, to explain the rupture in terms of a functional or structural change in the esophageal muscle. A prominent role is given to the failure of the tube to relax properly when a large volume of food and liquid is ejected. Among the structural factors are listed fixation of the esophagus at the hiatus, along the right pleura, the absence of voluntary muscle in the lower third, the curve of the esophagus to which may be added the points of entrance of esophageal arteries and the attachments of the esophagus to prevertebral fascia along the right posterior surface of the esophagus. Among the pathological changes which may contribute are mucosal erosions of variable origin, ulceration, esophagitis or recent as well as old alterations of the muscle. The alterations may be minimal and escape even a careful search.

An examination of all case records suggests to the present writers that no single mechanism is invariably responsible and presumably alterations of the mucosa, of the muscle or both, may be important in a particular instance.

The possibility of spontaneous rupture of the esophagus should be entertained when excruciating low substernal or high epigastric pain immediately follows vomiting. The pain may extend to the left chest, to the back or interscapular region. It is constant and scarcely influenced by morphine. Ordinarily vomiting is not repeated and swallowing may not be affected. The abdomen may be rigid to the level of the umbilicus but tenderness is often absent. Examination may be difficult when pain forces the patient to move continually or a sitting position is maintained. Shock rapidly supervenes.

Since a ruptured abdominal viscus is suspected owing to pain, rigidity and previous history of some patients, x-ray examination for subdiaphragmatic air is usually undertaken and proves negative. If films of the chest are obtained a mediastinal emphysema can be detected or, later, a rapidly accumulating left hydropneumothorax. Paracentesis of the pleural cavity yields gastric contents which are diagnostic if gastric herniation is excluded. Subsequently subcutaneous cervical emphysema appears; this is also pathognomonic for such emphysema develops in no other syndrome presenting a similar clinical picture.

Death occurs, as a rule, within 30 hours although two patients have survived for several days.

Definitive surgical treatment would be lifesaving if undertaken early.

CONCLUSION

A patient presenting the classical features of "spontaneous" rupture of the esophagus is presented. Necropsy findings indicate that the accident followed impaction of food with ulceration of the mucosa, esophageal abscesses, mediastinal perforation and necrosis with rupture into the left pleural cavity.

The pathogenesis and clinical picture of spontaneous rupture of the esophagus is discussed in order to attract attention to a catastrophe, the importance of which is not generally appreciated.

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A SOLUTION FOR THE PARENTERAL ADMINISTRATION OF CALCIUM

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CALCIUM IS THE most plentiful mineral constituent of the body, there being more than a kilogram of it in the skeleton (1). In comparison with this large mass, the blood contains an arithmetically insignificant amount—less than 300 milligrams (1). But this tiny quantity is of the utmost physiological importance.

The normal serum calcium level lies between 9 and 11 milligrams per 100 cc. (2). Of this, about 2.5 mgs. per 100 cc. exist as ionic calcium in equilibrium with the inorganic phosphate of the blood (3). About 4 mgs. per 100 cc. are combined with the blood proteins (4) and the rest occurs as an un-ionized complex, thought to be the citrate or some similar salt (5). This last fraction is apparently under the influence and control of the parathyroid hormone which enables the blood to dissolve more calcium than could be present because of the slight solubility of calcium phosphate (6).

All of these different calcium fractions are in equilibrium with each other. When we determine serum calcium, we obtain the total amount. It is technically almost impossible to determine the fractions not bound to protein—the physiologically active portion.

The proteins of the blood do not change appreciably except in profound metabolic disturbances. Eliminating this from our discussion, we may confine our attention to the physiologically active portion of the serum calcium. This represents about ½ of the total. Let us suppose that the serum calcium drops from 10 to 9 mgs. per 100 cc. This represents a loss of but 10%—not too great a burden for the adaptive powers of the body. But, under the conditions we postulated, that portion of the serum calcium that is combined with protein is unchanged. Therefore, the loss will fall entirely on the physiologically active portion. The relative loss will then be about 20%. Therefore, what might appear, at a first, uncritical glance, to be an insignificant drop in serum calcium could profoundly affect the physiological processes that depend on the serum calcium level. This might be the explanation to reconcile the divergence between the clinic and the laboratory for we often notice significant disturbances accompanied by only minimal changes in serum calcium. Furthermore, the clinical usefulness of calcium therapy is well established despite a failure to demonstrate any but slight changes in serum calcium.

Calcium salts have been used in the treatment of many conditions. They have been used empirically in the treatment of urticaria and other allergic states. Calcium increases the coagulability of the blood. It is indicated preoperatively—especially in liver and gall bladder surgery. Its antispasmodic action has been verified experimentally (7).

The "soothing" effect of calcium on the nervous system has not been fully explained. However, Scott and his associates have shown that the cells of the central nervous system have shells of some calcium-containing substance immediately within the cell membrane and just within the nucleus whose demonstration awaited the discovery of the electron microscope (8). We may indulge in a bit of pardonable speculation by likening these calcium shells to the rubber insulation on a group of wires and terminals in a complicated electrical circuit. When the insulation wears thin, the circuit develops spots of lowered resistance and an electrical impulse might spread beyond its desired path. In similar fashion, when the integrity of the calcium barrier is compromised, nervous impulses will spread. Bronk states that "the partial removal of calcium, for instance, makes a nerve more susceptible to the influence of other external agents; from this we may conclude that its presence gives stability to the cellular structure." (9).

Since the nervous system is bathed in blood, any diminution of ionized calcium in the serum would tend to wear away these calcium shells by osmotic action. This would give rise to increased cellular irritability. This may explain the clinically demonstrable antispasmodic action of calcium.

Replenishment of diminished serum calcium can be accomplished in several ways. Oral administration of soluble calcium salts is effective—but very slow. Most of the ingested calcium is precipitated in the bowel as phosphates, the carbonate and soaps. Only a small portion is absorbed. Therefore, while alimentary calcium suffices to insure skeletal growth and to maintain a physiological level in the blood, when there is need for an increase in serum calcium in a therapeutically reasonable time a more rapid absorption is essential.

The intravenous administration of calcium solutions

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effectively raises the serum calcium and that route is most frequently employed. Unfortunately, the effect is too transient, the added calcium being excreted into the urine within a few hours (10). Most of the commercially available calcium solutions cannot be given intramuscularly because they often produce painful indurations which sometime break down into slowly healing sloughs. The subcutaneous tissues are particularly sensitive and sloughing is the frequent sequela to leakage from the vein.

We have been interested in calcium deficiency states for a number of years. In a previous communication, we discussed the relationship between hyperinsulinism and hypocalcemia (11). We take the stand that the serum calcium level is optimally at least 10 mgs. per 100 cc. and that the generally accepted normal range of 9-11 includes many persons whose serum calcium concentrations are at least subclinically low. Our experience with many hundreds of patients has satisfied us that raising the serum calcium leads to greater subjective well being.

Calphosan (R)* is a specially prepared 1% solution of calcium lactate and calcium glycerophosphate in normal saline. It can be administered by any parenteral route. We have given it routinely in 10 cc. doses intragluteally.

*As furnished by The Carlton Corporation, New York City.

TABLE I.

DIAGNOSIS

Day of Experiment	Gastric Cancer	Bronchial Asthma	Urticaria	Hyperinsulinism (3 cases)		
1	7.7†	8.8†	8.3†	8.4†	8.7†	7.9†
3	10.7	11.4	10.7	11.0	11.0	9.3
5	10.5	10.4	10.7	9.2	10.6	10.4
8	9.2†	10.2†	8.8†	8.4†	9.1†	8.4†
10	11.0	11.6	10.8	11.0	10.8	10.7
12	10.2	11.0	10.0	10.0	10.6	10.4
15	8.6†	9.9†	8.7†	9.3†	8.4†	8.7†
17	11.4	11.0	11.0	11.1	10.3	10.4
19	9.8	10.6	11.2	10.8	10.0	10.9
22	9.9†	10.6†	9.9†	9.2†	8.8†	9.2†
24	11.4	11.2	9.7	10.0	11.3	11.0
26	11.0	10.7	9.3	9.8	10.2	10.7
29	10.2	10.8	9.8	10.4	9.4	10.0
36	9.8		10.2	10.6	8.3*	9.7
43	10.4	10.3		10.1	10.2	
50	11.0		11.5	9.7	10.1	10.0
57		10.6		10.0	10.0	9.5
Plus 1 mo.		10.6	10.5	10.0	8.4*	9.8
2 mos.		9.8	10.0	10.0	10.0	10.1
3 mos.		10.2	10.4	10.0	10.5	9.2
9 mos.		10.1	10.6	9.9	9.8	9.9

†—indicates an injection of Calphosan (R).

*—In the fifth case, it was necessary to give a few extra injections which were administered on the day following the determination of serum calcium.

The injections are absolutely painless and leave no indurations. Its pH is 7.2 whereas all the other commercial calcium solutions we were able to test had acidities ranging from 5.5 to 4.5. Of course, these are all 10% solutions and Calphosan (R) is only one tenth as concentrated. Dilution of the ordinary solutions to corresponding strength (i.e. with 9 volumes of water) should theoretically raise the pH by but one unit, which would still leave them too acid to be tolerated intramuscularly. The actual increase in pH was less than 1 because the buffer action of the salts mitigated the effect of dilution.

Calphosan (R) was tested for its efficacy in raising the serum calcium levels of persons with varying degrees of moderate hypocalcemia without regard to other diagnoses. The initial serum calcium was determined. Then an injection was given and the serum calcium was estimated every other day. The injections were given once a week for a month with analyses performed thrice weekly. Then the injections were stopped and the calcium determinations were continued at weekly intervals for another four weeks. Then the serum calcium was determined once a month for another three months and again after another six months. (Table I).

It soon became difficult to carry out this investigation as had been planned because the patients objected to the repeated venepunctures for the calcium determinations. Another group was therefore followed with weekly calcium estimations.

TABLE II

DIAGNOSIS

Week of Experiment.	Hypothyroidism	Hyperinsulinism (5 cases)				
1	8.2†	8.4†	8.0†	8.2†	7.8†	8.4†
2	9.4†	9.9†	9.0†	8.9†	8.6†	10.6†
3	9.2†	8.8†	8.3†	8.0†	8.9†	10.9†
4	9.8†	8.9†	8.2†	9.7†	8.3†	10.7†
5	9.6	9.5	8.6*	10.1	9.4*	10.8
6	8.4†	9.6	9.4*	9.8	8.7*	
7	9.8	9.7	9.2*	9.3*	9.0*	10.7
8		10.0	8.4*	10.1		10.2
Plus 1 mo.	9.7	9.3*	9.8	9.0*	10.3	10.2
2 mos.	10.2	9.5	10.0	10.4	10.0	10.2
3 mos.		9.8	10.2	10.2	9.7	10.8
9 mos.	10.6		10.4	9.9	10.1	10.7

†—indicates an injection on the day of the calcium determination.

*—indicates an injection on the day following the calcium determination. These were administered if the serum calcium fell below 9.5.

A third group of patients consented to the experiment only if the determinations were made at monthly

intervals. The injections were given once a week. Whenever the serum calcium fell below 9.5 mgs. per 100 cc., another series of four injections was administered.

TABLE III

DIAGNOSIS

Month of Experiment	Hyperinsulinism (3)			Hypothyroidism (2)		Menopause (2)		Urticaria (1)
1	8.8*	8.8*	8.2*	7.9*	7.8*	8.4*	8.0*	8.0*
2	10.7	10.8	9.6	8.7*	9.0*	9.8	8.4*	8.3*
3	10.8	10.3	10.0	9.8	10.4	9.0*	9.2*	9.0*
4	10.4	11.2	9.8	9.9	9.8	10.3	10.9	10.6
5	10.6	10.6		10.0	11.2			9.8
11	10.4	10.6	10.2		10.9	9.9	10.5	

*—indicates four weekly injections.

The determinations were done in duplicate by the method of Sobel and Sobel (12), the average being tabulated. In no case did the values differ by more than 0.3 mg. per 100 cc.

The efficacy of the preparation in elevating the serum calcium level is abundantly demonstrated by these tabulated analyses. In most cases, it was sufficient to administer but four weekly doses in order to establish isocalcemia which persisted throughout the period of observation (nearly a year). The 10 cc. dose contains but 16 milligrams of elemental calcium. When this tiny amount is dispersed in the 3.5 liters of serum (13), we should expect a maximum rise in serum calcium of but 16/35, or less than 0.5 mg. per 100 cc. However, elevations several times as great were obtained. The only available store of calcium being in the skeleton, the preparation must, in some way, mobilize some of the calcium in the bones to bring the concentration in the blood up to physiological values. As far as the bones are concerned, the loss of calcium is utterly insignificant.

Six persons with normal calcium levels (i.e., above 10 mgs. per 100 cc.) were injected with the material.

TABLE IV

Day of Experiment						
1	10.2*	11.0*	11.4*	10.8*	10.3*	10.2*
3	10.7	11.2	11.0	10.8	11.0	10.6
5	10.5	10.9	10.8	10.9	10.7	11.0
8	10.6*	10.8*	10.9*	10.6*	10.8*	10.8*
10	10.6	11.0	11.0	11.2	11.2	10.6
12	10.4	10.7	10.6	10.8	10.8	10.8
15	10.2*	10.8*	11.0*	11.0*	11.1*	10.9*
17	10.4	10.6	10.7	10.8	11.0	11.0
19		10.8	10.8	10.6	10.8	10.6
22	10.4*	10.9*	11.2*	11.0*	10.6*	10.6*
24	10.4	10.8		10.8	10.7	10.9
26	10.0	10.8	10.8	10.5		10.6

The results of this series of determinations could have been predicted. Under normal conditions, the blood is saturated with calcium. While it is possible to have any stable solution of any solute in any concentration up to saturation, supersaturated solutions are never permanently stable. Therefore, any tendency towards hypercalcemia would be corrected by increased excretion or deposition in the skeleton rather than solution of osseous calcium salts. This agrees with the rarity of hypercalcemia which is practically never found except in cases of hyperparathyroidism which is almost a clinical curiosity.

SUMMARY

Calphosan (R) has been found to be effective in raising low serum calcium levels. After four weekly injections of 10 cc., the level remained (in most cases) normal for almost a year. The injections were painless and produced no indurations or sloughs. The preparation was without effect on normal concentrations of serum calcium.

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PHARMACO-RADIOGRAPHY OF THE STOMACH AND DUODENUM

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PHARMACO-RADIOGRAPHY of the stomach and duodenum includes the use of all substances capable of modifying the behavior of the stomach. Of these substances, two main groups may be distinguished according to whether their action is stimulant or sedative.

For a long time sedatives (atropine, papaverine) have been in common use. The most useful ones however are those which stimulate the musculature of the stomach, ensuring a better moulding of parietal lesions, accentuating the mucosal relief and thereby making clearer lesions which could be no more than suspected on the standard series of radiographs: it is with this active pharmaco-radiography that we shall deal.

Pharmaco-radiography should in no event take the place of the recognized methods of examination of the stomach. It is a question of a complementary method which has indications and contra-indications. Just as in the study in thin layers and as with regulated compression, it should only be put into practice to clarify certain details remaining obscure on standard radiographies in total repletion.

HISTORY

The practical use of gastric hypertension and hyperkinesia induced by pharmacodynamic substances dates from 1943: P. Porcher, J. Levebvre, and B. Boudagian (1) after a muscular injection of morphine noted a stasis of the second portion of the duodenum and hypertension together with hyperkinesia of the stomach, between which the bulb was passively distended: it is the sign of induced duodenal stasis which these authors attributed to a modification of the behavior of Osschner's spincter.

Later we realized that the distension of the bulb was due more than anything to the flooding of the duodenum as a result of the rapid emptying of the stomach. In 1944 these same authors drew attention to the usefulness of gastric hyperkinesia induced by morphine in accentuating the movements of certain stomachs of slight contractility (5). In 1944 and 1945 with various collaborators, I tabulated the results of pharmaco-radiography with morphine on the pyloric canal, the antrum and on the lesser gastric curvature, (3, 6, 9) I advocated the introduction of morphine into the vein (10) and demonstrated the usefulness of this method in the study of incipient gastric cancer (7).

Other pharmacodynamic substances give results very closely resembling those of morphine. In 1944, Sénèque, Chiray, Gally, Le Canuet, and Grümler (4) used the tonic properties of ipecac in studying stasic stomachs. In 1946, with J. Renaux and E. Girard, we substituted venous injections of insulin for morphine (12). Up to that time, studies had been directed above all to abnormalities of outline, in particular that of the lesser curvature, on exposures in total repletion, and use was made of the increase in pressure of the baryta in the stomach due to the hypertension of the walls. In 1945 and 1946, I showed that insulin and above all morphine in venous injections could induce a hypertension of the muscularis mucosae which gathers up the mucous membrane and deepens its folds (7, 13); in 1948, I described the nature of the mucosal relief around the lesion, studied according to this method, both with malignant (16, 17) and with benign lesions (20).

TECHNIQUE

In all pharmaco-radiographical studies carried out so far, exposures in a procumbent posture and in total repletion have been used: It is by this method that the

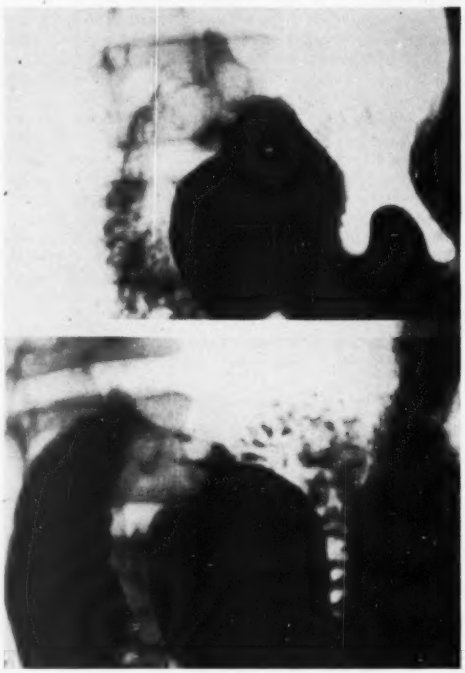

Fig. 1: Fibrous ulcer of the duodenal bulb.

Top: standard exposure. The bulb appears incomplete and irregular, partly concealed by the distended prepyloric antrum.

Bottom: pharmaco-radiography using morphine. The antrum, better toned, disappears. The second portion of the duodenum is extremely dilated. Between them the duodenum remains inextensible; but its form is clearly seen and a little spot which is probably a niche may even be observed.

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maximum effect is ensured and the most useful information obtained.

We make regular use of morphine and insulin, more rarely of ipecac.

Hypodermic injection of morphine.

10 milligrams of morphine hydrochloride are injected under the skin ten minutes before the ingestion of milk and baryta. The stomach must be sufficiently full of baryta. It is advisable to watch by radioscope for the appearance of hyperkinesia and hypertension induced by morphine, which sometimes occurs after a delay of 15 minutes. The exposures must be made quickly at the onset before the small intestine is flooded too much and the stomach too empty.

Venous injection of morphine.

5, sometimes 10 milligrams of morphine hydrochloride are injected into the vein. This injection should be performed preferably just before the ingestion of milk and baryta; but in certain circumstances, the injection may be made during the radiological examination when the stomach is relaxed. The venous injection has the further advantage of a speedier action than the subcutaneous injection: exposure can be made 5-10 minutes afterwards instead of from 10-25 minutes.

This method, like the preceding one, allows the study of abnormalities of outline on exposures in total repletion and in a procumbent posture. Furthermore, the rapid and drastic action of morphine allows a second examination to be performed using a gradually diminishing compression with a balloon, and a study of the state of the mucosal relief at the edges of certain lesions to be made.

Venous injection of insulin.

Its physiological action on the stomach has been known for a long time (Cannon, Jean Labarre, Bulatao); we used it in pharmaco-radiography by injecting 10 or 20 International Units of insulin into the veins, 5-10 minutes before the ingestion of milk and baryta: the waiting period is brief but variable and needs to be watched by x-ray. The exposures should be taken at the beginning of the insulin's action. There will be found to be a series of contractions each one of about 20 seconds duration, followed by intervals of complete rest of 40-50 seconds; the contractions, which are very effective, rapidly empty the stomach of its contents, producing a large dilation of the bulb and of the outline of the duodenum; later they become less frequent as the stomach empties. The violent contractions of the initial stages usually coincide with copious perspiration and when the patient remains standing, a slight feeling of lipothymia: it is the very best moment for x-ray pictures which should always be taken with the patient in a procumbent posture.

After the completion of the examination, the absorption of about 10 lumps of sugar and a sweetened meal together with a half-hour rest lying down will counteract the action of the insulin.

Oral administration of ipecac.

The patient may be given 40 grams of ipecac syrup the day before or the morning of the radiological examination; vomiting usually occurs and, for several hours, the stomach is in a temporary state of hypertension and hypermotility; this delayed action may exist even in the absence of vomiting.

40 grams of ipecacuanha syrup may likewise be mixed with the barium meal. A few minutes later the first waves of hyperkinesia appear. On certain occasions we have been able to use ipecac and morphine in conjunction.

PHARMACO-DYNAMIC ACTION AND ITS AFTER-EFFECTS

The action of these three substances is noticeably similar; it varies in its intensity and in its details. There can be observed:

1) gastric hypertension revealed externally by a reduction of the shadow surface of the horizontal portion of the stomach.

2) hyperkinesia of the stomach, with more or less rapid waves of concentration, often of a violent nature, proceeding from the direction of the angle of the greater curvature of the stomach.

3) hypertension of the muscularis mucosae with a gathering up of the folds of the stomach.

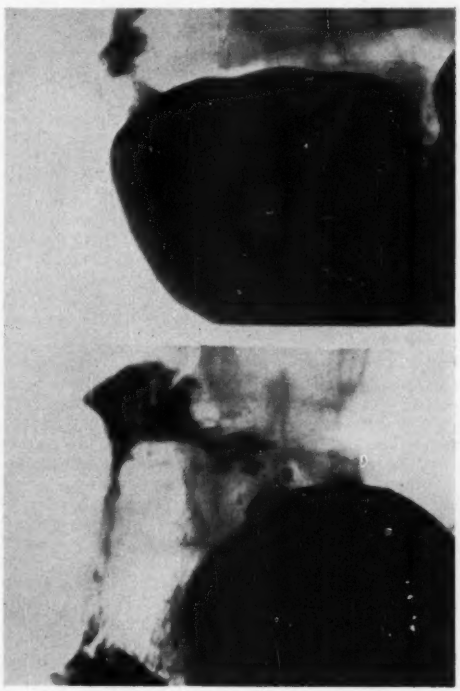

Fig. 2: Periduodenal tuberculosis.

Top: standard exposure. Distention of the antrum partially concealing the pyloric region. Bulb incompletely filled. Difficult duodenal passage.

Bottom: pharmaco-radiology using insulin. The expulsion of baryta shows up an irregular accordion-pleated bulbous constriction, a dilated genu superius and a second duodenal portion shortened by an external compression.

4) a more or less marked jejuno-duodenal dilation resulting from gastric hyperkinesia.

Pharmaco-radiographical action is particularly concerned with the horizontal portion of the stomach; gastric hypertension, which seems to us the most interesting effect is extremely clear and particularly constant with morphine and insulin administered by our method of venous injection.

Hyperkinesia induced by morphine is more violent and rapid than with insulin which is somewhat to its disadvantage. On the other hand, it is very slight with ipecac which constitutes a further inconvenience for the study of the duodenal bulb whose dilation is fairly instable with this last substance. The hypertension of the muscularis mucosae is particularly clear after venous injection of morphine.

Failures with this pharmaco-radiographic method vary according to the substance used. There may be said to be none at all with insulin; but the sensitiveness of patients to insulin is fairly variable and with the same dose a slight or a very marked effect may result.

As far as morphine is concerned, hypodermic injections show 8 to 10% of failures; in this event no hypertension and no hyperkinesia result—it is as if the stomach were paralyzed and it is in these cases of gastric inertia that patients vomit and feel ill. Venous injection of morphine fails much more rarely.

To the action of the two substances previously mentioned, ipecac adds its emetic action which may be used to empty certain stasic stomachs; its use is of course to be avoided with subjects who are particularly weak, those recently operated upon or after hemorrhage; the hypertonic and hyperkinetic action of this substance is less than that of morphine and of insulin.

The ill-effects and disadvantages of pharmaco-radiography are generally negligible. Let us first of all draw attention to lipothymia which rarely occurs (in 1% of cases) and that only when the patient is examined in an upright position: this examination being both useless and dangerous it is advisable to dispense with it. Elsewhere, the ill-effects vary according to the substance used and the mode of injection.

Hypodermic injections of morphine frequently cause nausea which may make the patient's return home difficult, and may be prolonged for several hours; there may be a persistent head-ache; in certain cases giddiness confines the patient to bed and often vomiting also takes place: it is for this reason that we usually ask our out-patients to bring a companion on the day of the radiography. Morphine by venous injection, which can be given in reduced doses and whose action is speedier, seems also to be eliminated more quickly: thus the immediate ill-effects (malaise, giddiness, drowsiness) occur earlier and the delayed ill-effects are either absent or lessened.

Let us draw attention to the fact that J. Arnous, L. Jourde and R. Daliphard (18) think that the emetic action of morphine is due to the influence of a peroxidasic substance which brings about the transformation of morphine into oxide of morphine, and they endeavor to prevent this oxidation by adding to the morphine Vitamin C whose powerful reducing action is well-known; to 5 milligrams of morphine injected into the vein they add 0.25 gr. of ascorbic acid in a 10% solution; in this way they appear to have considerably reduced the ill-effects due to intolerance.

In the case of venous injections of insulin, we have already mentioned the copious perspiration which accompanies gastric hyperkinesia and the hypoglycemia which conditions it. At the conclusion of the examination, the patient may be subject to drowsiness and a feeling of asthenia and faintness; but in general, nausea and vomiting are never experienced. Moreover the consumption of sugar and a half-hour rest lying down put an end to any feeling of distress: after this lapse

Fig. 3: Duodenal ulcer, pyloric ulcer with fibrosis, muscular hyperplasia of the pyloric ring and ulcer of the lesser curve of the antrum.

Top: standard exposure. The prepyloric antrum is narrowed; it is difficult to situate the pylorus exactly; the duodenal tract is scarcely distinguishable.

Bottom: pharmaco-radiography using venus injection of morphine. The well-filled bulb presents a deformity typical of an ulcer. The pyloric canal is abnormally long and rigid and presents a niche on its left edge. Finally the hypertonic filling of the antrum moulds a little niche of the lesser prepyloric curvature perfectly.

of time the patient may quite well go home without experiencing any further ill-effects.

Ipecac has the disadvantage of usually causing vomiting and nausea; its more pronounced ill-effects and its lesser hypertonic action on the stomach make it less useful than morphine and insulin.

In short, from the comparison of the results and disadvantages of each one of these three substances a conclusion as to their usefulness may already be drawn. In practice, I regularly use venous injections of insulin whose very constant results and complete harmlessness are an advantage, notably with patients in town. I keep venous injections of morphine for cases in which it is necessary to obtain a very violent hypertension and particularly of the muscularis mucosae. I rarely use ipecac except for stasic stomachs.

PHARMACO-RADIOGRAPHICAL RESULTS

The results with these different pharmacodynamic agents vary slightly according to the position of the lesion under study and according to its nature.

1—Pharmaco-radiography of the duodenum. It was in the study of the duodenal bulb that this method was first put into practice. It is mainly applied in the case of invisible and irregular bulbs. Morphine and insulin may be used indifferently.

Invisibility of the bulb on standard exposures may be due to functional causes (spasmodic intolerance of the bulb, gastric inertia) to organic causes (ulceration of the bulb, duodenitis, duodenal polyposis).

Morphine and insulin remove the invisibility of the bulb due to functional causes, secure a good repletion of the bulb, in this way showing it up in its entirety.

When, after pharmaco-radiography the bulb does not dilate it may be concluded that there is a strong likelihood of an ulcer around which the duodenal wall has been retracted; the bulbous region generally appears as a small passage contrasting with the violent contractions of the stomach on the one hand, and on the other with a considerable dilation of the second portion of the duodenum. Often there occurs a dilation of the bulbous zones, which have remained supple, accentuating the deformities typical of ulcer of the bulb. Finally, the ulcerated bulb itself will very frequently be made prominent due to endocavitary hyperpressure (figs. 1 and 3).

Irregularity of the duodenal bulb is also indicated by pharmaco-radiography which allows the organic origin of these deformities to be confirmed. On the ulcerated, atresic, inextensible bulbs, morphine and insulin always, as a result of endocavitary hyperpressure, mould the lesion perfectly, and allow an estimate of the importance of the niche and of the fibrous deformities to be made.

It happens that a fibrous ulcer of the duodenal bulb may be drawn back behind an antrum which conceals it by its sub-pyloric distention, proof of the onset of difficulty in emptying the stomach.

In general, pharmaco-radiography, by inducing hypertension of the antrum, helps to contract the antrum and free a little of the bulb it was concealing, thereby facilitating the taking of exposures.

The cases in which pharmaco-radiography ensures a diagnosis of functional ailments of the bulb, of ulcus or of acute duodenitis are numberless. But the method has its disadvantages and it must not be forgotten that in a few cases it could hide a frontal niche by encouraging excessive repletion of the duodenal bulb: this serves to impress once more the need for making standard exposures first of all and the usefulness of pharmaco-radiography and regulated compression in conjunction at bulb level.

Lesions of the second portion of the duodenum will often benefit from pharmaco-radiography which ensures good moulding of an ulcer situated low down, of a tumor or of an extrinsic compression as in the tuberculosis case we have observed (fig. 2).

2—Pharmaco-radiography of the stomach. Pharmaco-radiography of the duodenal bulb consisted above all of using a violent emptying of the stomach to distend and fill bulbs which were incompletely moulded during ordinary examination. Pharmaco-radiography of the stomach makes use of more refined pharmaceutical methods and its interpretation is more subtle.

The action and results of pharmacodynamic agents vary somewhat according to the position of the lesion under study.

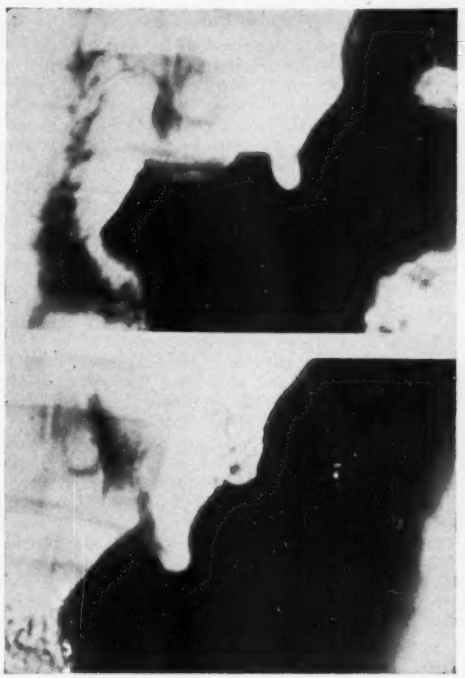

Fig. 1: Callous ulcer of the lesser prepyloric curvature.

Top: standard exposure. The prepyloric region is blurred. The pylorus and the duodenum are badly filled.

Bottom: pharmaco-radiography by venous injection of morphine carried out during the same examination. Good moulding of the prepyloric region and of the pyloric canal showing a prepyloric niche and a segmentary rigidity which is continued on the canal.

Pyloric canal. At this level, in particular, powerful expulsion from the antrum which both morphine and insulin induce will be used; it is in this way that these two substances usually show up a niche in the canal (fig. 3) invisible with an ordinary exposure, allow the organic origin of an irregularity of the pyloric canal and of the antrum immediately prepyloric to be seen clearly—whether it be a question of a sugar-loaf and irregular shaped pylorus consistent with a small cancer in its initial stages or of the double bracket shaped pylorus (pylore en parenthèses adossées) consistent with congenital or acquired muscular hyperplasia of the pylorus, or even of the glove finger appearance of fibro-muscular atresia of the prepyloric antrum.

Prepyloric antrum. Pharmaco-radiography gives clear results and its diagnostic value is great when confronted with abnormalities of the antrum immediately prepyloric. At this level it may prove difficult to distinguish secondary functional lesions from an ulcer at the angle or from an external affection (cholecystitis, typhlitis and appendicitis) of organic lesions; moreover very tiny lesions of the antrum may be accompanied by important organo-functional aspects which conceal their presence. Now, the anti-spasmodics (atropine, papaverine) do not cause these spasmodic deformities of the antrum to disappear with any regularity; on the contrary, insulin and morphine, by the hyperkinesia and hypertension which they induce, have a tendency to increase the pressure of the baryta in the prepyloric antrum, to show up its outlines clearly and to make deformities of a functional order disappear. This moulding of the outlines of the antrum may be fleeting, therefore it should be quickly recorded in a series of exposures; depending on the case, it will facilitate observation of a clearly contracted antrum having a normal outline, or on the contrary deformed on all the films by a niche or a constant rigidity which may be superimposable on all the negatives and indicate an organic lesion (fig. 4).

Horizontal and angular lesser curvature. When faced with a lesion on the lesser horizontal curvature or of the angle of this lesser curvature, one may be inclined to use sometimes one and sometimes the other of the pharmacodynamic effects of morphine and insulin. It is advisable to know these effects thoroughly in order to interpret the negatives. Sometimes, as in the positions dealt with above, the negatives to concentrate on in particular are those on which inter-cavitary hypertension moulds the outline of the walls of the stomach perfectly allowing a tiny lesion, invisible on ordinary negatives, to be discovered, or the detailed examination of a deformity of the outline or an indication of its extent (fig. 5). To obtain its full effect, this research should of course be carried out during total repletion of the stomach.

At other times the use of hyperkinesia is preferable in the study of negatives showing violent gastric contractions so that the suppleness of the walls of the stomach can be more fully appreciated, and the permanent nature of the lesion shown, and so that small segmentary rigidities may be revealed.

Finally, the hypertension of the muscularis mucosae always adds its action to that of the two preceding ones. The action of morphine and insulin on this muscularis mucosae has already appeared to me particularly clear where there is a chronic irritation already in existence: this explains the elective action of pharmaco-radiography on the niches and on the perilesional mucosal relief.

As far as the niches are concerned, their tops are known to correspond with the ulceration, their middle portion with mucous covered walls, raised up by the edematous swelling of the edges, and their base with a circular contraction of the muscularis mucosae around the lesion. The niche appears then externally to be a sort of pit at the bottom of which is the ulceration, whose walls and surronds are due to perilesional modifications partly organic (edema, sclerosis) and partly functional (contraction of the muscularis mucosae). The action of the morphine and of the insulin on the niche is in contrast with that of atropine and papaverine. The latter have a tendency to lessen the niches by diminishing the contraction of the muscularis mucosae; morphine and insulin on the other hand accentuate the depth of the pit on top of the ulceration, both by the hypertension of the neighboring muscles and by the increased pressure of the contrasting liquid.

For the study of the mucosal relief on the periphery of a niche or of an infiltrated lesion, pharmaco-radiography and regulated compression are used in conjunction. Hypertension of the muscularis mucosae gathers together the mucous folds and this action is more marked at points where there exists a chronic irritation, and this helps to accentuate abnormalities of the relief, bringing them into sight when they are tiny or concealed. Regulated compression, by drawing together the walls of the stomach facilitates this throwing into relief of the outline. In this way attention can be drawn to signs of marginal lip, the convergence of folds, or drapes can be induced and, above all, the normal or abnormal nature of folds converging on a lesion can be appreciated, and this provides useful arguments in establishing an early diagnosis of cancer of the stomach.

It is quite evident that these hypertonic effects of pharmaco-radiography using insulin and morphine are not to be employed in the case of stomachs naturally hypertonic and which empty rapidly. With stomachs of normal or subnormal tonicity and motility, these two substances increase the efficiency of the diagnosis in all cases, whether it be a question of examining a deformity more closely, of noting its extent, or of an attempt to make small lesions visible.

It will be seen that according to the case in point, whether the abnormality is a niche or an infiltrated aspect, whether it is a question of an ulcer or of a cancer or of gastritis, the complex effects of pharmaco-radiography may be used in very different ways.

USE OF PHARMACO-RADIOGRAPHY IN THE EARLY DIAGNOSIS OF CANCER OF THE STOMACH

The advent of pharmaco-radiography represented a considerable improvement in the early diagnosis of gastric cancer. However it does not dispense either with the standard radiological examination in total repletion, or with the radio-clinical method, or with R. A. Gutmann's therapeutic test; it completes them. If, in fact, one tries to analyze the technique by which a clinical radio diagnosis of cancer of the stomach in its initial stages is established, it is seen that it proceeds from a series of many arguments graded and grouped

together; two stages of this diagnosis may be considered. There is in fact firstly a diagnosis of suspicion and later a formal diagnosis. The formal diagnosis of incipient cancer is of course based, in the main, on radio-clinical method and on a therapeutic test without which one only makes oneself liable to dangerous mistakes. But this stage of etiological diagnosis is always preceded by a stage of diagnosis of suspicions which is based on the form of the radiological abnormalities.

During this first stage of tracking down or diagnosis of suspicions (and throughout the radio-clinical investigation) the quality of the abnormal radiological images intervenes in the discussion; thus any improvement in the quality of the images, any method likely to reveal details in greater number and more clearly on the negatives, helps to facilitate the diagnosis.

Now, depending on the way it is used, pharmaco-radiography allows two types of radiological anomalies to be studied in detail and it is on these that the radio-clinical deduction is partly based: that of the outline of the stomach and that of the mucosal relief.

The deformities of the outline of the lesser curvature which the negatives in total repletion reveal are certainly the most useful in diagnosis; it is these abnormalities which arouse early suspicions of cancer as has been clearly shown by R. A. Gutmann and by Garcia Calderon.

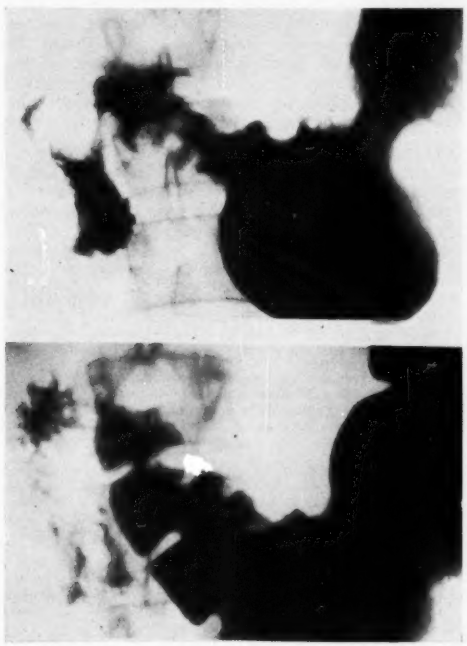

Fig. 5: Callous ulcer of the lesser curvature beneath the incisura angularis.

Top: standard exposure. The lesser sub-angular curvature shows a deficit of constant filling on all the exposures and several protrusions in this lacunary aspect. The prepyloric is narrow and accordion shaped and as though worm-eaten. A cancer is to be feared.

Bottom: pharmaco-radiography using ipecac. The peristaltic contractions become normal; the increased tonus moulds perfectly an ordinary niche of the lesser curvature. The antrum still shows large transversal folds but the pseudo-lacunary images have disappeared.

Pharmaco-radiography is of the greatest usefulness in the detailed study of abnormalities of outline on the negatives in repletion.

The first aim in analyzing the niches is intercavitary hypertension which reduces the volume of the stomach while maintaining the normal dimensions of the lesion, and puts the niche into better relief. At the same time, hypertension of the muscularis mucosae will induce a contraction of the muscles at the base of the niche which because of this become more prominent. It is in this way that we have shown examples of benign niches whose imperfect moulding gives the outline of the lesser curvature on all standard negatives, a worm-eaten multi-lacunary appearance suggestive of cancer; pharmaco-radiography moulded perfectly one of the ordinary niches (fig. 5).

Inversely, countless cases of incipient gastric cancer in which pharmaco-radiography, on a stomach outline appreciably normal or just slightly rigid or presenting a pitted surface suggestive in itself, revealed abnormalities typical of a slight lesion in the form of a little recessed niche (niche encastrée), of a plateau shaped niche or of a niche in an arc-shaped space (niche dans une lacune en arc), even more suggestive (fig. 6).

Under other circumstances, the violent waves of contraction of the periods of hyperkinesia would be expected to show in contrast certain segmentary rigidities.

Study of the mucosal relief around the lesion will generally only be carried out in a second examination after a suspected abnormality of the stomach outline has been traced on the exposures in total repletion. For this we used regulated compression in conjunction with pharmaco-radiography using morphine or insulin. This combined method seems to us particularly useful in the case of infiltrated forms of incipient gastric cancer which are characterized by the precocious nature of the sclerous paratumoral retraction; it is particularly marked when the lesion under study is situated in the horizontal broad portion of the body of the stomach.

The morphology of the folds converging on the lesion is likely to provide useful arguments for establishing a diagnosis: in incipient gastric cancer the folds are generally abnormally large, ending in a club shape, do not reach the lesion and are fixed in their form; on the contrary, in certain benign lesions difficult to diagnose (as with certain ulcer scars or certain areas of atrophic gastritis) the folds converge as far as the lesion, keep their suppleness and their mobility and above all, do not present any abnormally great modification in volume.

PHARMACO-RADIOGRAPHY IN THE STUDY OF GASTRO-ENTEROSTOMISED STOMACHS.

It is well known how difficult it can be to study the horizontal portion of the stomach when the drainage is working well. A compression of the mouth of gastro-enterostomy is often insufficient to obtain a good moulding of the short-circuited region at the level of which a tumor's existence is suspected. Pharmaco-radiography

generally releases a violent baryta expulsion which allows the functioning of the orifice and of the antrum to be studied at the same time.

CONCLUSIONS

By using the pharmacodynamic action of different substances the quality of radiographic exposures of the stomach can easily and regularly be improved and their instructiveness increased.

Sedatives, atropine and papaverine in particular, may prove useful in relaxing certain spasms of the pylorus. However, hypertonic substances, and in particular morphine and insulin, are of the greatest service.

Pharmaco-radiography with insulin and morphine acts by inducing hypertension in the gastric cavity, hyperkinesia of the stomach, hypertension of the muscularis mucosae and secondarily a jejuno-duodenal dilation as a result of gastric hyperkinesia.

In the study of the duodenal bulb and of the second portion of the duodenum, when the bulb is invisible or when it is irregular or when the second portion of the duodenum is suspected, venous injections of morphine and insulin will allow the segment of intestine to be moulded and distended, for the relief of lesions to be seen in detail when they exist or their absence to be confirmed.

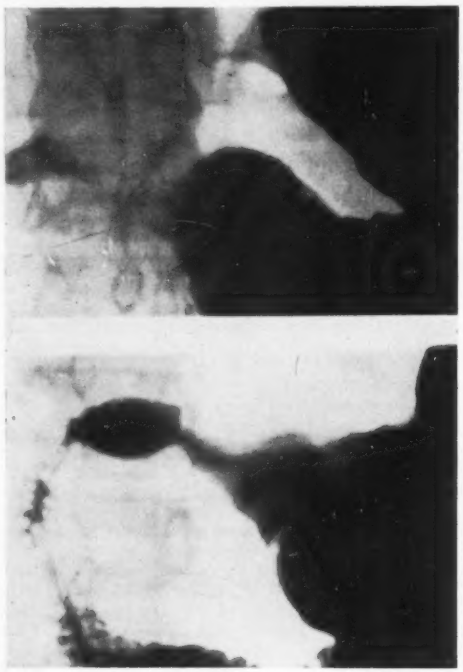

Fig. 6: Epithelioma of the mucous membrane, the muscularis mucosae remaining unaffected.

Top: standard exposure. There is a recess with segmentary rigidity of the lesser curvature.

Bottom: pharmaco-radiography with hypodermic injections of morphine. The injection of morphine was carried out during the same examination. The hypertension due to morphine moulds the deformities of the horizontal segment of the stomach which is seen in the form of a plateau-shaped niche whose bottom is semi-rigid. The folds converge on the lesion. The antrum is contracted.

The same technique will generally enable lesions of the pyloric canal and of the prepyloric antrum to be shown.

On a level with the horizontal and angular portion of the lesser curvature, the hypertonic action of morphine and insulin may help the moulding of slight abnormalities; in certain cases it induces violent peristaltic waves which may prove a hindrance in the study of the small niches; but, on the other hand this hyperkinesia may be used to show in greater detail certain localized rigidities. Pharmaco-radiography can be useful in the study of the antro-pyloric region of certain gastro-enterostomised stomachs.

It considerably facilitates detection and study of suspicious signs of incipient gastric cancer, either by moulding perfectly and showing up the superficial erosions such as the plateau-shaped niche and the niche in an arc-shaped space, or by emphasizing the contrast between certain infiltrated rigidities and the supple wall of the stomach or by allowing the mucosal relief around these lesions to be studied and signs of malignancy such as the convergence of permanent, abnormally large folds ending in a club shape to be sought.

This is a complementary method which should not in any event replace the recognized methods to total repletion, but which equally as well as study in thin layers or regulated compression, may give in a second examination, a much truer diagnosis.

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ABSTRACTS ON NUTRITION

YOSHIOKA, M., OGUCHI, M., KYSE, T., YAMAO T. AND SENO, S.: *Iron and hemoglobin metabolism. III. Some biological studies and hematopoietic action of asparagin-iron compound.* J. Mie Med. College, I, 2, Nov. 1950, 105-120.

The authors produced excellent improvements in hypochromic anemia in humans using a compound of iron and asparagin. (They say practically nothing about how this compound was made, and refer to it as ASP-Fe). The compound was nontoxic intravenously, excess being rapidly excreted by the kidney and intestine. The daily administration of ASP-Fe to anemic patients showed remarkable hematopoietic response, and body weights increased rapidly at the rate of 4 kilograms per month. During the period of ASP-Fe treatment, reticulocyte responses were not observed; on the contrary reticulocytes rapidly decreased after the compound was administered. They feel that the presence of reticulocytes is not an indication of blood regeneration but of iron deficiency. This constitutes a decidedly radical viewpoint.

KOUNTZ, W. B.: *Revitalization of tissue and nutrition in older individuals.* Ann. Int. Med., 35, 51, Nov. 1951, 1055-1067.

Kountz studied 60 women whose ages ranged from 50 to 95 years. He found that the use of estradiol benzoate, 1 mg. twice a week, plus progesterone *or* testosterone, 5 mg. daily, intramuscularly, had a distinct revitalizing influence on the endometrium and the vessels of the uterus. The rejuvenating effect was not limited to the uterus but was found in the skin, the muscles and the nasal mucosa. This revitalizing effect did not produce malignancy or other disease if the doses were held within physiological bonds. Arteriosclerosis did not interfere with this rejuvenating effect, but rather the arteriosclerotic factor seemed to lessen, which suggests that certain forms of arterial degeneration may be the result of physiological inactivity, e.g. in the uterus. The primary action of the estrogenic and endrogenic substances was a direct effect on bodily nutrition. One result was retardation of both the mental and physical decline.

GRAHAM, D. M., LYON, T. P., GOFMAN, J. W., JONES, H. B., YANKLEY, A., SIMONTON, S. AND WHITE, S.: *Blood lipids and human atherosclerosis. II. The influence of heparin upon lipoprotein metabolism.* Circulation, IV, 5, Nov. 1951, 606-673.

Heparin administered to rabbits and man causes profound reorientation in the distribution of low density lipoproteins, characterized by a shift of lipoproteins of high Sf rates to those of successively lower Sf rates. Heparin administered to cholesterol-fed rabbits prevents the development of high levels of Sf 10-50 lipoproteins and retards the development of atherosclerosis in such animals. Following heparin administration the plasma contains an "active principle" associated with ultracentrifugal globulins, which produces similar reorientation of the lipoprotein spectrum *in vitro*. Heparin added directly to serum is ineffective *in vitro*. Intermittent heparin administration to patients with severe angina pectoris results in dramatic and uniform relief from this symptom for periods of several days beyond a single injection in 55 of 59 patients. Sodium heparin, 50 to 100 mg. per week, was used intravenously or intramuscularly.

SHERRILL, J. W.: *Diabetic retinitis: the relationship between retinal degenerative changes and the degree of diabetic control.* Bull. Scripps Metabolic Clinic, 2, 6, Oct. 1951.

Among the earliest organic changes found in diabetes is the appearance of capillary micro-aneurysms in the perimacular area of the retinae. He feels that retinal changes can be retarded for many years if treatment of diabetes is efficient. He presents a group of diabetics under treatment from 20 to 30 years who have normal vision because they were faithful to treatment. He restricts principally fats in the diet and uses enough insulin to prevent glycosuria and hyperglycemia. He is drastically opposed to "free dieting."

JACOBS, E. C.: *Oculo-oro-genital syndrome: a deficiency disease.* Ann. Int. Med., 35, 5, Nov. 1951, 1049-1051.

The oculo-oro-genital syndrome is a component of pellagra and was seen during the last war in Bataan and Corregidor in 1942. Scrotal dermatitis at one time affected 75 percent of the 8,000 American prisoners who were on starvation rations. When glossitis and angular stomatitis appeared in these same patients, its pellagrous nature became apparent. Conjunctivitis, varying from mild to severe, developed in 93 of 100 moderately advanced cases selected for study. As no medicines were available, treatment was nil and there was lost an excellent opportunity to determine the component of vitamin B complex to whose absence the oculo-oro-genital syndrome was due.

Two months of adequate diet brought marked improvement. The syndrome is thought to be closely associated with pellagra, but not pellagra itself.

KLAVERAN, F. W.: *Folic acid.* J. Indian Med. Assn., XX, 12, Sept. 1951, 439-446.

This is a clinico-chemical paper devoted to the practical aspects of folic acid and its interrelationships with other vitamins. An interesting point made is to the effect that folic acid causes neurological complications only in Addisonian pernicious anemia and not in other anemias. He feels that the organism normally requires both folic acid and the liver principle (vitamin B_{12}) for its normal function. The Wills factor evidently is not identical with folic acid. Folic acid has revolutionized the treatment of the sprue syndrome. He concludes that health requires the harmonious interaction of all vitamins,—a harmony which may be disturbed by deficiencies or by high doses of individual vitamins.

HILDRETH, E. A., HILDRETH, D. M. AND MELLINKOFF, S. M.: *Principles of a low fat diet.* Circulation, IV, 6, Dec. 1951, 899-904.

The authors note that in prescribing low fat, low cholesterol diets clinically for the purpose of preventing or benefitting arteriosclerosis, too little attention has been paid to vegetable fats which, although they contain no cholesterol, actually raise the serum cholesterol concentration. Hence, restriction of both animal and vegetable fat seems indicated if the serum cholesterol is to be reduced. Restricting cholesterol alone does no good unless the total fat also is restricted simultaneously. Restricting total fat is of greater importance in reducing the serum cholesterol than in reducing the intake of cholesterol. Actually the former automatically reduces the latter.

Such therapeutic low-fat diets must be individualized. The authors start normocholesterol subjects on 25 to 30 gm. fat diets. If, after a month, the serum cholesterol concentration has not decreased, fat is further restricted. Hypercholesterol subjects may have to be restricted to a 10 gm. per day fat diet. The article should be consulted for specimen diets.

GREENBERG, A., DAVIES, H. L. AND BLAIR, J. L.: *Diabetic gangrene.*

Gangrene in the diabetic is extremely amenable to conservative surgery, and a radical amputation should never be done as a routine measure. Control of infection is of paramount importance, yet the diabetic state stimulates the formation of collateral circulation which is usually well established when the crisis of peripheral vascular thrombosis appears. If no bone necrosis is present, nibbling surgery is performed and necrotic tissue is thoroughly excised.

SANCETTA, S. M., AYRES, P. R. AND SCOTT, R. W.: *The use of vitamin B_{12} in the management of the neurological manifestations of diabetes mellitus, with notes on the administration of massive doses.* Ann. Int. Med., 35, 5, Nov. 1951, 1028-1048.

In a series of 12 patients showing the neurological manifestations associated with diabetes, and treated with crystalline vitamin B_{12} intramuscularly to the exclusion of therapy other than insulin and diet, 3 showed complete neurological remission, 3 improved and, in 2 cases, the improvement was questionable. Usually 15y to 30y were given daily for 7 to 14 days, followed by a maintenance dose of 15y to 30y once or twice weekly. Massive doses of B_{12} (as much as 1000y intravenously) did not seem to carry a cumulative effect and should be reserved for the rare patient completely refractory to small doses. Paresthesias disappeared, sluggish knee kicks improved, ataxia disappeared, shooting pains disappeared, chronic normocytic anemia in one case was cured. Possibly thiamin interferes with this remarkable effect of vitamin B_{12}.

KLOPPER, A. AND VENTURA, S.: *Iron metabolism in pregnancy.* B. M. J., Nov. 24, 1951, 1251-1254.

In late pregnancy, iron-deficiency states are difficult to assess by ordinary hematological investigations. The levels of serum iron, the iron-binding capacity of the serum proteins, the serum copper, and the protoporphyrin were investigated in normochromic anemia and in hypochromic anemia. In true iron-deficiency states these show a characteristic pattern which is quite different from the normal. Out of 46 cases of anemia, 43 were caused by disorders of iron metabolism, the majority being classical cases of microcytic hypochromic anemia which were readily corrected by the intravenous administration of iron. The preparation used was "ferrivenin." Nothing is said about reactions following such intravenous injections. Hemosiderosis is avoided by giving an amount of iron calculated from the degree of deficiency.

EDITORIAL

THE POSSIBILITY OF LIVER DYSFUNCTION IN ALLERGY

Recent work that we have been engaged in has convinced us that some allergic reactions are based, at least in part, on an increased, but perhaps perverted, function of the liver. This may be termed "hyperhepatism," and together with liver damage may be considered as a form of liver dysfunction much like "hypersplenism" is a splenic dysfunction.

The concept of liver dysfunction in allergy is not new. In fact, the liver was thought to be involved in the days when the concept of allergy was first stated but has since been lightly regarded (1). Present evidence forces us to seriously reconsider the possibility.

The allergic reaction most often studied experimentally has been anaphylactic shock. Admittedly, anaphylaxis in the different species appears to involve different organs. In spite of this fact, much of the mechanism of action can still be learned by analysis of the findings in animals.

It has long been known that histamine liberated during anaphylactic shock was an important cause of the symptomatology noted in this condition. Anaphylaxis in the dog is characterized by a fall in blood pressure and decreased blood coagulability. Manwaring (2) proved years ago that the liver was necessary for the production of anaphylactic shock in the dog. He was able to transfer anaphylaxis from one dog to another by cross circulation methods, but could not produce anaphylaxis if the liver was excluded from the circulation. He was able to prove that the rapid fall of blood pressure in the dog was due to the rapid liberation of a depressor substance from the liver. Dragstedt (3) concluded that the vaso-depressor substance was histamine.

However, histamine could not be responsible for the diminished coagulability of the blood which is a characteristic of anaphylactic shock in dogs. Jacques and Waters (4) showed that heparin is released from the liver during anaphylaxis. Code (5) feels that during this state, there is a simultaneous liberation of histamine and heparin from the liver, resulting from cellular disruption there. He further believes that there is another factor besides histamine, and this is sensitized cell damage elsewhere caused by the antigen-antibody reaction. Histamine may be incidentally released as a result of this cell damage, depending on the cell content.

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Thus histamine may be liberated by cell damage throughout the body.

There is evidence, then, that the liver and tissue cells are both involved in anaphylaxis and the allergic process. It should be noted that in the dog, most of the reaction occurs in the liver, which may not be the case in other species, including man. Theoretically, at least, (to benefit certain allergic phenomena in patients) we must inhibit some of the activities of the liver, and also those of certain sensitized tissue cells.

The allergic reaction may be divided conveniently into an immunological part and a pharmacodynamic part. The immunological part which starts with the first exposure of the cell to the allergen and continues through the formation of intracellular antibodies, the re-exposure of the sensitized cell to the same allergen, the reaction between the allergen and the antibody and finally the cell injury. Following these stages come the pharmacodynamic events, with the manufacture and release of the H-substance and other substances, e.g., heparin in the dog, then the attack of the H-substance on the shock organ, the response of the shock organ and finally the allergic symptoms. The immunological part of the reaction certainly takes place in the reticuloendothelial system, and notably the liver. The elaboration of the H-substance and the release of this substance certainly also takes place largely in the reticuloendothelial sytem. Of course, it also occurs elsewhere, but nature is never so uneconomical as to allow a delicate, specialized reaction in an organ not specifically prepared for it. It has been shown by early workers that even if the entire amount of blood is replaced by blood from another animal, anaphylactic shock is still possible (6). Thus the antibody-antigen reaction does not occur in the blood stream.

Antibodies are specific proteins and appear to reside in the gamma or euglobulin fraction. Antibody globulins are in all probability formed in the same sites as blood proteins are formed. These sites have not been finally determined, but there is increasing evidence that the reticuloendothelial system participates and that the liver plays a major role.

When an antigen is injected in humans, antibodies can be demonstrated in the blood within several days and reaches a maximum in 7 days. Continuing the injection produces a high antibody titre to such a point, that further administration does not raise it. However, smaller doses of antigen can maintain this high titre. Again, if the injections are stopped for a sufficient time, the titre will fall to a low level, but readministration of the antigen will elicit an accelerated and more marked response in antibody formation.

There appears to be evidence that the reticulo-endothelial system, especially the liver, retains the ability to form specific antibodies, and does it in a more extensive way than it did originally, i.e., a greater response to a lesser stimulus. This reaction could be considered a form of "hyperhepatism."

It is well known that ACTH and Cortisone act in an extremely salutary fashion in severe hypersensitivity reactions such as status asthmaticas and drug reactions. We have documented elsewhere (7) our theory that these hormones work at least, in part, by "occupying" certain of the liver functions. Briefly, Hench first noted that remissions in rheumatoid arthritis occurred during pregnancy and during hepatitis. In both of these conditions there exists a state of hepatic dysfunction. From time to time, case reports appear in the literature that show that severe asthma and nephrosis are benefited by a coincident hepatitis, in other words, by liver dysfunction. It appears likely that in these states, some increased, but perverted function of the liver exists, that is reduced during hepatitis, and the patient improves. We are not listing all the evidence here that we have, that ACTH and Cortisone probably act by "occupying" one or more of the liver functions, because we have done this on several other occasions (7).

Recently, we have obtained satisfactory results in severe serum-sickness type of penicillin reactions with sodium dehydrocholate (8). (An unconjugated sodium salt of an oxidized bile acid).

We can adduce evidence to show that sodium dehydrocholate depresses some of the liver functions, even though it does not cause actual liver damage. On the contrary, there is much experimental and clinical evidence that dehydrocholic acid and sodium dehydrocholate improved the overall function of the liver. Schwiegk (9) found that the administration of sodium dehydrocholate markedly increased the rate of blood flow through the hepatic artery, as measured by a stromuhr. Grodins, Osborne, Ivy and Goldman (10) reported that sodium dehydrocholate increased the blood flow through the hepatic artery from 10% to 218%, with an average of 48%. They also found, in addition to the increased hepatic blood flow, that there was an average increase of bile flow of 700%.

However, the volume of bile is not the only important consideration. Thus Schmidt (11) and co-workers found that the natural conjugated bile salts produced a true choleresis in dogs, as both the *volume* and *constituents* of the bile were increased in amount, while the unconjugated ketocholanic acid preparations (as sodium dehydrocholate or dehydrocholic acid) increased the *volume* of the bile, but, significantly, the total amount of bile salts, pigment and cholesterol was *decreased*. Inasmuch as there was an absolute decrease in the synthesis of the natural constituents of the bile, Schmidt and his co-workers posed the possibility that sodium dehydrocholate is an *hepatotoxic* agent since it depresses some hepatic functions. However, we know from much clinical and experimental experience that sodium dehydrocholate given over prolonged periods of time does not result in hepatic injury. Thus we must conclude that even though sodium dehydrocholate may improve overall liver function as measured by the hippuric acid, bromsulfalein and bilirubin clearance tests, there are some functions that it must depress. We feel that one of these functions is the ability of the liver to mediate anaphylactic shock or similar allergic reactions.

Finally, we would like to call attention to the fact that anaphylactic shock can be temporarily eliminated by a variety of physical measures (surgery, performance of severe muscular exercise, induced hyperpyrexia) and chemical factors, such as narcotic drugs and blockade of the reticulo-endothelial system with India ink or colloid dyes (12). The one result that all these measures have in common is a depression of liver function. If, then, anaphylactic shock and perhaps other allergic phenomena are examples of "hyperhepa-

tism," then reducing some of the liver functions by chemical or physical means may temporarily, or in some cases permanently, eliminate the abnormal responses.

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Samuel Waldman, M. D., F. A. C. P.

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BOOK REVIEWS

A STUDY OF ANTIMETABOLITES. D. W. Woolley, B. Sc., Ph. D. John Wiley & Sons, Inc., 1951, New York City, $5.00.

Woolley, formerly of the University of Alberta, then of the University of Wisconsin, and now a member of the Rockefeller Institute for medical research, well-known for his efforts to isolate, describe and study the action of vitamins and other nutrients, has produced a book of 270 pages devoted to substances which produce deficiency diseases in living organisms. Most of the antimetabolites are covered and the author offers explanations of their mode of action, even in normal physiological processes. No doubt the information gathered together in this volume will help in the treatment of obdurate diseases. Antimetabolites, furthermore, are already serving a useful function in helping to solve the nature of biochemical processes.

A TRANSLATION OF GALEN'S HYGIENE (DE SANITATE TUENDA). Robert Montraville Green, M. D., Charles C. Thomas, Springfield, Ill.

This is the first translation of Galen's book into any modern language. It is beautifully printed and bound. The book itself is extremely interesting, especially to those devoted to the history of medicine. Galen was one of the most remarkable figures in medicine. His anatomy was correct, although his physiology and pathology were, of necessity, speculative. His therapy is at least vastly interesting even though it stands in such strange contrast to modern regimes. On the personal side, Galen suffered from a marked inflation of the ego, which is perhaps an essential to one who wrote some 750 books, most of them on medicine. The translator and the publisher are to be congratulated on producing a rarely valuable and charming book.

DEFICIENCY DISEASES IN JAPANESE PRISON CAMPS. Dean A. Smith and Michael F. A. Woodruff. (Medical Research Council special report series, No. 274). H. M. Stationery Office, Publications Division, 429 Oxford St., London, W. 1, England. 6 shillings, 6 pence.

The authors of this very valuable report were medical officers who were themselves prisoners of the Japanese. Very careful clinical observations were made and herein reported on all the various kinds of malnutrition encountered and, although the authors were working always without a decent supply of foods *or* vitamins, their observations are not of less, but possibly greater value for that reason alone. One of their chief conclusions was that it is impossible to overestimate the value which a poor diet of the Asiatic type derives from the addition of beans, rice polishings, peanuts, yeast and abundant green vegetables. The comparatively low mortality in the camps which is disclosed in this report was due largely to the production, purchase and careful utilization of these food materials.

This voluminous and skillful report leaves the reader, incidentally, in a mood of sadness, but it also increases his interest in nutritional disease because the authors have reported their unbiased findings which, of course, do not always, if ever, agree precisely with what is now formally taught and accepted about certain deficiency diseases.

They found that for the type of population under consideration, doing the type of work described, in an equatorial climate, weight loss occurred when the mean caloric intake fell below a level of 2,000 to 2,100 calories daily, except in as far as weight loss was marked by weight increase due to the development of edema. They specify four types of nutritional edema,—(1) edema of cardiac beriberi with congestive heart failure, (2) edema in beriberi of peripheral origin without heart failure, (3) edema of hypoproteinemia, and (4) edema occurring in states of general malnutrition in which there is no evidence of beriberi, in which the plasma protein level is normal and to which the name is given of "isohydric famine edema."

More thiamine was needed to prevent beriberi than commonly realized. In cardiac beriberi, although adequately treated with massive doses of thiamine, the authors in a considerable number of cases noted sudden death, due to acute cardiac arrest or ventricular fibrillation, although those cases had presented only presumably minor disorders of rhythm. It can only be supposed that some associated deficiency was present which produced an early irreversible myocardial change, despite all treatment, including abundant thiamine. They note individual idiosyncracy, such that, if a group of apparently similar men in similar circumstances, on diets similarly deficient in thiamine, one gets neuritis, another edema, a third dies suddenly of heart failure, while a fourth remains apparently perfectly well. Obviously there are individual differences in minimum dietary requirements, efficiency of utilization and other functions, but the true nature of these differences is at present a mystery.

In pellagra, nicotinic acid deficiency is clearly of fundamental importance, but the authors note that the use of considerable quantities of maize (corn) in one camp was associated with increased incidence of pellagra. The "zeistic hypothesis" which assumes the presence of a toxic substance in maize, though discredited for many years, has regained support through experiments showing that maize contains a factor pellagragenic to the rat. The authors describe also the P syndrome—dermal and oral lesions, indistinguishable from those of pellagra, allergy specific to black beans, leucopenia or agranulocytosis, responding to "marmite" and rice polishings.

One of the outstanding features of deficiency diseases in Japanese camps was the prevalence of disorders of the nervous system, and these were responsible for the great majority of the *permanent* disabilities resulting from imprisonment in the Far East, suggesting a possible nutritional basis for a number of neurological disorders whose etiology still is obscure, but which have not hitherto been considered to have any relation to nutrition. Among those to be considered were peripheral neuritis. Wernicke's superior hemorrhagic encephalitis (usually responding to thiamine and/or B-complex), spastic paraplegia, and retrobulbar neuropathy (often associated with vitamin B_2 deficiency).

The "burning feet" syndrome sometimes has an independent existence and is probably due to a specific lack of pantothenic acid.

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The report includes 3 valuable appendices and a good reference list.

VISCERAL INNERVATION AND ITS RELATION TO PERSONALITY. Albert Kuntz, Ph. D., M. D., Charles C. Thomas, Springfield, Ill., Nov. 1951, $4.50.

Kuntz's definition of "personality" is the sum total of the characteristics of the individual, involving his body as well as his mind and his feeling as well as his thinking. This connotation of the word is similar to its usage in ancient India and may, indeed, be more desirable than our popular use of the word to indicate purely mental and emotional characteristics. The parts of the book which deal with the anatomy and physiology of the visceral nerves are admirable and could hardly have been written by anyone except a Professor of Anatomy. For this reason alone, anyone desiring an unusually good clarification of modern concepts of adrenergic and cholinergic innervation should avail himself of the volume. In the section on "Visceral neural factors in personality" there is also much of real value but Kuntz is devoted to the idea that, inasmuch as impulses emanating from the viscera influence the higher psychic processes, and inasmuch as the thinking of the individual is conditioned by his emotional feeling, it follows that thought is greatly influenced by the viscera. Is this not, in its essence, still a philosophical problem? It is acceptable that there exists a constant, if unconscious, bombardment of the brain by visceral stimuli, but it certainly is a moot question how much influence such stimuli exert on purely intellectual processes, e.g., esthetic choice of casuistic judgment. The reviewer while willing to accept the "personality" as an integrated whole in which visceral stimuli are not without influence of some sort upon the mind, still adheres to the common conception that there is a definite autonomy in mental processes. To believe that "the visceral urges still remain the mainsprings of conduct" is a concept which Kuntz hastens to modify in the case of man. Intellectual voluntary control of conduct and intelligently planned cultivation of the emotions and the intellect are, as he states, a distinctive characteristic of human personality. The book represents an intricate and highly specialized assessment of the influence of the viscera on mind, and, because of its logical deductions and clarity of style, should not be overlooked by psychiatrists, as well as clinicians generally.

BIOLOGICAL ANTAGONISM. Gustav J. Martin, Sc. D., 516 pages, The Blakiston Co., Philadelphia, 1951, $8.50.

For those whose knowledge of biochemistry is meager, Martin's book is difficult reading. It is a concise presentation of the "theory of biological relativity," which underlies all biological activity and is fundamental to the solving of all biological problems. Biological antagonism is reflected in natural and synthetic displacing agents, and occurs in the fields of amino acids, purines, pyrimidines, vitamins, hormones and minerals, and forms the basis of immunology, pharmacology, and chemotherapy. Martin offers the concept of biological relativity based on extensive study of these antagonisms. He concludes that there are no *absolutes* in biological systems which might distinguish them from physical systems. Every phase of biology is relative and there are no absolutes except *time*. No single molecular structure possesses a function not shared in some degree by structurally related molecules. Biological order is actually based upon disorder, upon antagonism. Biological systems represent the end results of chance. In the broadest sense, biological antagonism is a manifestation of competition between moieties for surface position on proteins.

THE LAMP IS LIT. The Pan American Sanitary Bureau, Washington, 1951.

The present brochure, written by Ritchie Calder, is the story of the World Health Organization (WHO) written in a sketchy, popular and anecdotal fashion which anyone might profit from reading. In three years this organization has accomplished a great deal more, in various parts of the globe, than one would have thought possible.

Books Received:

SURGERY OF THE ESOPHAGUS. J. L. Lortat-Jacob. Editions Medicales Flammarion, 22 rue de Vangirard, Paris VI, France. Price 4.800 francs. A paper-bound edition covering the whole title subject, with a preface by Prof. F. D'Allaines.

SURGICAL TREATMENT OF RECTAL CANCER. Prof. F. D'Allaines. A paper-bound edition well illustrated and constituting a distinguished monograph on the title subject. Editions Medicales Flammarion, 22 rue de Vangirard, Paris, VI, France. Price 5.700 francs.

No. 1 and No. 2. Revue Internationale d'hepatologie, a new bimonthly journal, representing the continuation of La Revue du Foie and of the Bulletin of the Association for the physiopathologic studies of the liver and of nutrition. Exclusive agent: F. C. Couppie, 8 rue d'Ulm, Paris, France. Foreign subscription price per year 2.400 francs.

GENERAL ABSTRACTS

TWISS, RUSSELL J., CARTER, R. FRANKLIN, AND FISHMAN, BENJAMIN S.: *Infection in chronic cholecystitis.* J. A. M. A. 147, 13, 1226. Nov. 24, 1951.

The study was made of 259 patients with chronic cholecystitis coming to operation. Preoperative and postoperative cultures of the duodenal bile were obtained, as well as cultures from all parts of the biliary tract at operation. Operative cultures were positive in 73 (28%), and were sterile in all parts of the biliary tract in 186 (72%) of the patients. The sterile and the infected groups had a similar incidence of symptoms and abnormal physical findings, as well as the same percentages of abnormal cholecystograms. Gross and microscopic pathologic examination showed no significant differences in the sterile and infected groups.

In the group of 186 patients sterile in all parts of the biliary tract at operation, the results of preoperative duodenal drainages in 100 patients gave one or more sterile cultures in 85% of those with free hydrochloric acid and in 61% of those having no free hydrochloric acid. Fifty patients with sterile preoperative cultures, practically all having free acid, remained sterile postoperatively. Of 32 patients having no free hydrochloric acid, 10 showed postoperative positive cultures of duodenal bile.

In the group of 73 patients with pathogenic organisms in the biliary tract at operation, the predominating organisms were Escheria coli, Salmonella typhosa, nonhemolytic Streptococcus, alpha hemolytic Streptococcus (green), Klebsiella pneumoniae (Friedlander), and Proteus vulgaris. Stones were positive in 31 of 52 cases, the common duct bile and cystic node cultures were positive in all but one case each. 87% showed pathogenic organisms in the preoperative drainage. The six patients having sterile preoperative cultures had sterile gallbladder bile at operation. Postoperative drainages showed sterile cultures of duodenal bile in 10 out of eleven typhoid carriers and in all patients having free acid with pure colon or streptococcus infections. In the majority of the patients having no free acid and in those having acid with mixed cultures at operation, the duodenal bile remained positive.

In both the sterile and the infected groups, there was the same incidence and type of pathological changes and stones, suggesting that infection was superimposed upon previously existing pathological conditions. The presence of active infection, however, makes the condition of the patient more serious. Infectious cholecystitis can be cured only if treated in the early stages by cholecystectomy. The early recognition of biliary tract infection is for the most part dependent upon the demonstration of pathogenic organisms in the duodenal bile. With suitable sterile precautions this can be done accurately in the majority of patients.

Franz J. Lust.

FABRYKANT, MAXIMILIAN, ASHE, BENJAMIN I., AND ALLEN, JULIA F.: *Arteriovenous distribution of glucose in spon-*

taneous hypoglycemia. Proc. Am. Diabetes Ass. 10, 116. 1950.

Arteriovenous distribution of sugar was studied in twelve patients with a clinical history of spontaneous hypoglycemia. Determinations of true glucose were made in the course of oral and intravenous glucose tolerance tests as well as during spontaneous hypoglycemic episodes. The relation between the hypoglycemic manifestations and the blood sugar variations was carefully noted. The development and the intensity of hypoglycemic episodes were found to be well correlated with the level of the arterial blood sugar. The glucose tolerance tests as currently confined to two or three hours of observation are inadequate to establish a diagnosis of spontaneous hypoglycemia. The hypoglycemic reactions become manifest when the test is carried out for five hours or longer.

The authors conclude that the study of the arterial blood sugar is of considerable importance for the diagnosis of hypoglycemic states. The use of venous blood alone may yield conflicting results.

Franz J. Lust.

SCHORR, SAMUEL AND SCHWARTZ, ARMIN: *The roentgenological manifestations of amebiasis of the liver with concomitant findings in the chest.* Am. J. Roentgen. and Rad. Th. 66, 4, 546. Oct. 51.

The authors studied 49 cases roentgenologically. The first changes are limited to an enlargement of the liver shadow, elevation of the right leaf of the diaphragm and restriction of its mobility. The changes might correspond to amebic hepatitis without chest involvement. A localized bulging of the right diaphragm into the lower right lung field denotes a solitary liver abscess. Chest involvement comprises obliteration of the costo-phrenic or cardio-phrenic sinuses, pleural effusion, and pneumonic consolidation with or without abscess formation. A linear stringlike perpendicular shadow may be seen in the right lower lung field in addition to a fixed and deformed diaphragm. This last roentgen finding might be an additional aid in the diagnosis of amebiasis of the chest and worthy of further studies. When dealing with pathology of the right side of the chest, the possibility of amebiasis of the chest should always be borne in mind, particularly in countries where amebiasis is endemic.

Franz J. Lust.

RITVO, MAX, COTTER, THOMAS P., ZAMCHECK, NORMAN: *Early roentgen diagnosis in acute bleeding from the upper gastro-intestinal tract.* Am. J. Roentgen. and Rad. Th. 66, 5, 728. Nov. 51.

The authors studied 52 patients. Emergency roentgen examination of the esophagus, stomach and duodenum was carried out as early as possible. Roentgen studies were performed in 42% of the patients within 24 hours; in 63.5% within 48 hours; and in 83% in less than 72 hours, after admission to the hospital.

The roentgen studies were not performed in routine fashion but were individualized according to the condition of the patient. It was the author's practice to make the examination as complete and detailed as possible. The patients were divided into three categories: those too ill to stand (3 patients); those able to stand but whose condition precluded the use of mechanical pressure (44 patients); and those in whom complete roentgen study including palpation and mechanical pressure was possible (5 patients).

Small amounts of opaque meal proved more satisfactory for the demonstration of most lesions. The roentgen techniques are discussed. Only four patients of the entire group showed evidence of continued or recurrent bleeding after examination. In no instance were there any serious complications or sequelae attributable to the roentgen studies. The early examination is of great benefit to the patient.

Dr. Franz J. Lust.

LEVIN, EMANUEL, J. AND FELSON, BENJAMIN: *Asymptomatic Gastric Mucosal Prolapse.* Radiology 57, 4, 514. October 1951.

The authors performed roentgenological studies of the upper gastrointestinal tract in 100 patients who had no gastrointestinal symptoms.

Gastric mucosal prolapse was encountered in 18 cases. The prolapse was slight in ten, moderate in five, and marked in three patients. No significant increase in frequency of prolapsed mucosa was encountered in any particular systemic disease.

Because of the high incidence of this finding in patients without symptoms, Levin and Felson concluded that the clinical significance of gastric prolapse has been overemphasized, and that it is seldom the cause of symptoms.

Franz J. Lust.

ARIEL, IRVING M.: *The effect of single massive doses of roentgen radiation upon the liver.* Radiology 57, 4, 561. Oct. 51.

The effect of single massive doses of roentgen rays (300r to 100,000r at 90 kv) involves all of the component parts of the liver. Edema, hyperemia, and leukocytic infiltration probably are a manifestation of damage to the vascular system. Why edema appears to be most marked in the central part of the lobule and polymorphonuclear leukocytic infiltration in the portal areas is not evident.

The liver cells are damaged or destroyed in proportion to the dosage, very high dosage causing complete necrosis while the lower dosage produces only slight evidence of damage (swelling). In the lower dosage range, focal destruction of the liver cells is produced, indicating apparently a variable sensitivity to radiation. Repair is rapid when possible; otherwise death occurs, depending upon the dosage and extent of the damage.

Franz J. Lust.

KRIEGER, A. (St. Gallen, Switzerland): *Die akute solitäre Magenerosion Dieulafoy mit tödlicher Massenblutung. (The gastric solitary erosion of Dieulafoy with fatal bleeding).* Schweiz. Med. Wschr.; 7. Oct. 1950, vol. 80, No. 40; 1070-1073.

The famous French physician Dieulafoy described in 1897 the so-called "exulceratio simplex" which consists of an acute and solitary erosion of the stomach. This erosion produces an unexpected and massive bleeding, which is usually deadly. Dieulafoy thought that this "exulceratio" was the first stage of a peptic ulcer, the death of the patient preventing its development.

K. reviews the 18 published cases and tries to describe the clinical aspect of this disease. It appears at any age, more often in men, until then in perfect health. In 3 cases only the fatal hemorrhage had been preceded, a few years ago, by important bleedings; but usually the gastrorrhagia occurs again at short intervals and is fatal. The symptoms are very scarce, not even an epigastric pain!

By macroscopic examination, the ulceration reaches the submucosa; its edges are not indurated and the surrounding mucous membrane is normal. By the microscope, one finds in the submucosa a winding artery with a diameter of 1-1,5 mm., and often herniated towards the inside of the stomach. Hence, the development of an "exulceratio simplex" needs the coincidence of an erosion and of a subjacent curved blood vessel.

Although the ulceration starts first, the blood vessel's arrosion afterwards, K. does not believe that the exulceratio simplex is the first stage of a peptic ulcer, as it is located on the sides of the stomach and not on the lesser curvature, and as the gastric juice is not hyperchlorhydric.

The only treatment is the immediate operation; blood transfusions are ineffective.

M. Demole (Geneva)

HESS, W. ET V.RUTTE, B, (Basel, Switzerland): *Die intermittierende und perforierende Pancreacyste. (Intermittent perforated cyst of the pancreas).* Schweiz. med. Wschr.; 6 Mai 1950; vol. 80, No. 18; 476-479.

The authors give the clinical history of two cases of this very rare disease and make a review of publications on intermittent pancreatic cysts and of perforation of pancreatic cysts, followed by complete healing or by an aggravation of the patient's condition.

In the first case, a woman of 73 had the symptoms of acute pancreatic necrosis and pleural effusion. Later, a tumor developed in the left superior part of the abdomen; 7 days later, this tumor disappeared when the patient vomited an amount of fetid liquid; but in the same time, an important intestinal bleeding killed the patient. The necropsy showed a cyst in the tail of the pancreas, which had perforated in the stomach and in the left lung.

The second patient was a young woman of 21 who had suffered for two years from acute abdominal attacks, with a high level of amylase in the blood and urine. A new attack was accompanied by the development of a fluctuant tumor in the left superior part of the abdomen. This tumor disappeared several times when the patient felt violent pains and evacuated liquid stools. A cholecystectomy did not heal the patient, so H. practiced a kind of marsupialization which revealed all the symptoms, although leaving a pancreatic insufficiency.

M. Demole (Geneva)

GORDON-MULLER, TH. (Geneva): *La sécrétion totale de l'acide chlorhydrique dans l'interprétation des chimismes gastriques. (Total hydrochloric acid secretion, as a new way of interpreting gastric test meals).* Thesis, Geneva, N° 2044, (1951).

The results of the gastric test meals having disappointed many physicians, G. tried, after the few authors who have searched before her, to calculate the total number of mgm. of HCL produced by the stomach in 1 hour (instead of drawing the curve of secretion or appreciating its highest level).

Having performed 388 gastric test meals on all kinds of digestive patients, and comparing this new way of interpreting the test to the previous ones, G. concludes that the total amount of HCL secreted in 1 hour shows that:

1. it differentiates clearly the duodenal ulcers from all other diseases, by its higher total HCL.

2. the gastric ulcers are not actually hyperchlorhydric, as the high level reached sometimes does not coincide with a high total of HCL.

3. many patients with gallbladder diseases, gastritis or functional dyspepsia have sometimes a gastric curve with a high peak, but actually a low total, acid rate.

M. Demole (Geneva)

GAILLAND, L. ET DEMOLE, M. (Geneva, Switzerland): *Rectocolite ulcéreuse avec insuffisance surrénale traitée par la Cortisone. (Ulcerous colitis with suprarenal insufficiency treated by Cortisone).* Acta Gastrico-Enterologica Belgia; avril 1951; vol. XIV, No. 4; 223-231.

Before reporting a successfully treated case, the authors discuss the participation of endocrinal factors in the pathogenesis of ulcerous colitis. The relationship of this disease with the feminine genital cycle is unquestionable, but did not give any therapeutical indications. On the other hand, there is no evidence of constant relationship with the suprarenal cortex, according to the specific tests, and the treatment with this hormone has been more often unsuccessful than otherwise, in clinical cases. The use of Cortisone and ACTH can therefore be considered as contestable.

In the case here related, a young woman of 30 years developed the disease a short time after giving birth to a fifth child, and, three months later, the condition is that of an acute form, with general infective phenomena (10.400 W. B. C.). Arterial hypotension, pigmentation and asthenia speak in favor of a suprarenal cortical insufficiency and the laboratory tests (dosage of blood steroids; epinephrin and ACTH test; Keppler water-test) confirm this diagnosis.

The treatment started, the first 10 days with 200 mgm. Cortisone and was continued for a month with 100 mgm. pro die (total 4 gm.), combined with 5 mgm. desoxycorticosterone (Percortene). Although signs of hypercorticism (swelling of the face; increased weight (5 kgm); superior labial hypertrichosis; hypertension up to 190), were evident, the ulcerous colitis disappeared completely, and the patient's recovery seems to be lasting.

KIRSNER, J. B., PALMER, W. L., LEVIN, E. AND KLUTZ, A. P.: *Gastric antacid and anti-secretory drugs: a survey based primarily on their effects upon gastric secretion in man.* Ann. Int. Med., 35, 4, Oct. 1951, 785-811.

None of the available antacids completely neutralizes the free acidity in man for prolonged periods. Calcium carbonate in hourly doses of 2 to 4 gm. along with milk and cream and with atropine in doses of 1.0 mg. 2 to 4 times daily, usually maintains the pH of gastric contents between 4.0 and 5.5 in patients with duodenal ulcer and does not produce alkalosis. This regimen is only effective during the period of administration. The continuous intragastric drip is more effective but its applicability is limited. Aluminum hydroxide, magnesium trisilicate or tribasic calcium phosphate in large quantities diminish but do not completely eliminate free acidity. Protein hydrolysates are less effective than calcium carbonate. Resins, detergents and mucin do not give impressive results. Enterogastrone is variable and unpredictable. Hormonal treatment is unimpressive. Atropine varies widely in its effects. Some of the other cholinergic blocking agents are promising,—tetraethylammonium salts, hexamethonium compounds and especially banthine. The authors have noted recurrence of ulcer during banthine treatment. They hope that continued research will yield a method for the sustained elimination of free acid in the stomach of man and believe that this will provide the solution to the problem of peptic ulcer.

WALLACE, F. T., UTTERMAN, W. F. AND STANTON, A. M.: *Indications for cholecystectomy.* J. Southern Med. & Surg., CIII, 3, Aug. 1951, 249-250.

The interpretation of gallbladder x-ray films is not always easy. The non-filling of the bladder by the dye may be due to a blocking of the cystic duct, so that, in such a case, the urgency for surgery would be greater than where one merely had a non-filling from other causes. In such a case the decision to operate would have to be made on clinical grounds. Where stones are present in the gall bladder, the operation of cholecystectomy is advisable to prevent the development of such complications as cholangitis, common duct obstruction, secondary liver damage and pancreatitis, as well as carcinoma of the gall bladder in one percent. If the gallbladder fills and no stones are demonstrated, *no surgery should be done.* Stones were present in 95 out of 100 cases of cholecystectomy. There was no mortality. The authors do not believe that infection is a factor in the development of stones. Sometimes small stones may be found at operation which did not show up in the x-rays. Thus, such cases, if they have colic, should be subjected to operation.

SODEMAN, W. A., DOERNER, A. A., GORDON, E. M. AND GILLIKIN, C. M.: *Chloroquin in hepatic amebiasis.* Ann. Int. Med., 35, 2, Aug. 1951, 331-41.

The effectiveness of chloroquin in hepatic amebiasis has been clearly confirmed. Primary failure of the drug in 3 patients (out of 7) with subsequent success establishes the fact that this drug, like emetine, is not always effective, and that a failure to respond to therapy is not necessarily an index of nonamebic hepatic involvement. Refractoriness to chloroquin in certain stages of hepatic abscess is described, although the drug was later successful. No evidences of serious chloroquin toxicity were noted in this series of seven cases.

PRUGH, D. G.: *A preliminary report on the role of emotional factors in idiopathic celiac disease.* Psychosomatic Med., XIII, 4, July-Aug. 1951, 220-241.

14 cases of idiopathic celiac disease were studied from a psychological standpoint. A consistent though nonspecific personality type of an anxious rigid, moderately compulsive nature has been noted among the mothers of such children. Prior to the onset of the disease there was evidence in all cases of an emotional disturbance in the children due to a conflict between anger and resentment toward the mother on the one hand and increased dependent need for affection and support on the other. Remissions have sometimes appeared as a result of resolution of such conflicts. Psychotherapy of the mothers has been of definite value to the children's welfare.

UNDERDAHL, L. O.: *Addison's disease versus fatigue states.* Miss. Valley Med. J., 73, 4, July 1951, 112-116.

This is an excellent practical review of the symptoms, signs and treatment of Addison's disease. As the author points out, small doses of cortisone in addition to D. C. A. seem to be effective in treatment.

JACOBSON, G. AND CARTER, R. A.: *Small intestinal rupture due to non-penetrating abdominal injury.* Amer. J. Roent. and Rad. Ther., 66, 1, July 1951, 52-64.

The authors present 19 cases of rupture of the small bowel due to non-penetrating abdominal injury. Retroperitoneal perforation of the duodenum was manifested by an outlining of the kidney by gas. Free subphrenic gas was demonstrated in only two cases of ruptured jejunum and in none of the ileum. The marked paucity of positive findings makes the roentgen examination of the abdomen of little value in excluding perforations of the small intestine following non-penetrating abdominal injuries.

BEGTRUP, H.: *Medical indications for the surgical treatment of acutely bleeding peptic ulcer.* Brit. Med. J., July 7, 1951, 20-22.

Among 7,254 patients treated during a 7 year period, 127 had hematemesis. In 115 cases the hemorrhage was caused by peptic ulcer, and 21 of these patients died, 19 as a result of ulcer bleeding, i.e., a mortality rate of 16.5 percent. Pederson's criteria for surgical intervention are—age over 50; hematemesis at hospital: recognized ulcer. Bohn's criteria are,—age over 40, when two or more of the following are fulfilled,—good evidence of ulcer, especially gastric ulcer; hematemesis at the hospital; severe hemorrhage. By applying these criteria to the present statistics, it was seen that Bohn's criteria must be regarded as suitable for determining which patients are to be operated on at once.

TURNBULL, R. B., FISHER, E. R. AND ROSENAK, B. D.: *Primary linitis plastica carcinoma of the colon.* Cleveland Clin. Quart., 18, 3, July 1951, 210-216.

The authors report a case of primary linitis plastica type of carcinoma of the colon arising in a previously existing ulcerative colitis. The patient was diagnosed as ulcerative colitis in 1931 but he remaned well until 1943, when his symptoms returned and the barium enema showed absence of haustral markings throughout. Symptoms recurred in 1947 but for 2 years he was kept under control with sulfasuxidine. A severe exacerbation occurred in 1950, at which time the sigmoid showed striking narrowing for a distance of 16 cms., and appeared contracted. In 1951 the left colon and sigmoid were removed and a left transverse colostomy done. He gained 20 pounds and is able to work. Pathological examination showed an adenocarcinoma of the colon: extensive linear and stenosing type,—linitis plastica.

DR. EDUARDO ECHEVERRIA, (Central Army Hospital, México City, Méx.): *Esophageal resection for cancer of the upper third.* Revista de Gastroenterología, Tomo XVI Núm. 93. Mayo-Junio-1951.

A case is presented of a 57 year old male with a two-year history of progressive dysphagia and hoarseness of three months duration. Diagnosis of carcinoma of the esophagus was made by esophagoscopy and X-rays and confirmed by biopsy. The lesion was at the level of the aortic arch.

Through ample thoracotomy incision (with removal of the 7th and 8th ribs) the esophagus was dissected free up to the base of the neck. The tumor involved the left recurrent nerve but was not attached to the aorta. The abdomen was entered through the diaphragm and the stomach was dissected free, preserving both the right gastric and right gastroepiploic arteries. This completed, the stomach was brought into the chest and the defect of the diaphragm was closed around the pylorus. Transection of the esophagus at the cardia was effected and both ends closed. Following this, the thorax was closed and a new incision was made along the anterior border of the left sterno-mastoid muscle. The thoracic esophagus was pulled into the field through the supraclavicular orifice and section of the cervical esophagus was done about 1 cm. below the lower level of the hypopharynx. Through the same supraclavicular orifice the stomach was brought into the neck and anastomosed to the remaining esophagus in two layers. The wound was closed without drainage.

During the immediate post-operative period hypertensive crises occurred frequently. The patient required oxygen administration for several weeks. Forty-five days after surgery emergency tracheotomy was performed because of flooding of the bronchi by aspirated vomitus; subsequently the evolution of the patient has been satisfactory (eight months of follow up).

The author comments on the importance of practicing exploratory thoracotomy even in cases judged inoperable on clinical grounds, since this opinion can be reversed with the thorax opened. In his opinion only patients with positive biopsy should be subjected to operation.

The liberal use of intravenous procaine during surgery is necessary to prevent vago-vagal reflexes.

Finally he mentions that in cases with esophago-gastric anastomosis at neck level, emergency bronchial aspiration and tracheotomy may have to be performed, and that routine tracheotomy may prove to be a convenient measure.

PEARSON, C. C. AND MELLINGER, G. W.: *The non-functioning gallbladder.* Bull. Mason Clin., 5, 3, Sept. 1951, 90-95.

The x-ray report of a non-functioning gallbladder should stimulate the clinician to try to explain the result, to consider the possibility of such things as technical errors in carrying out the test, intrinsic gastrointestinal disorders preventing absorption of the dye, hepatic disorders resulting in lack of concentration of the dye in the gallbladder and certain other less common conditions. The x-ray picture of the gallbladder should be repeated after elimination or correction of other causes of non-visualization. A non-functioning gall bladder on repeated x-ray after consideration of the above factors means intrinsic biliary tract disease, usually gall stones, in practically all cases.

GOSLINGS, J., HIJMANS, W., QUERIDO, A. AND KASSENAAR, A. A. H.: *Further experiences with prolonged treatment of rheumatoid arthritis with A.C.T.H. and gold.* Brit. Med. J., Sept. 22, 1951, 698-702.

The authors found in prolonged treatment of rheumatoid arthritis with A.C.T.H. that invariably a relapse occurred on discontinuation of this treatment. In a few cases the improvement obtained with A.C.T.H. could be maintained by concomitant gold therapy.

In a recent group of patients, an initial period of striking improvement was followed by the onset of a refractory state. The authors advance several possible reasons for this refractoriness but come to no conclusion. They still feel that the use of A.C.T.H. in rheumatoid arthritis is worthy of further investigation in spite of the fact that 100 percent successes with A.C.T.H. or cortisone are never obtained.

ELECTROLYTE METABOLISM

Observations suggesting that the edema of congestive heart failure results from an initial retention of water rather than sodium are reported by Dr. George E. Miller, Department of Medicine, University of Buffalo School of Medicine, in Circulation, The Journal of the American Heart Association (4: 270-277, 1951).

The article, *Water and Electrolyte Metabolism in Congestive Heart Failure*, describes metabolic balance studies of sodium and chloride carried out in eight subjects recovering from congestive heart failure. The loss of water from extracellular fluid was noted to be proportionately much greater than decrease in sodium and chloride content. It is concluded that some of the water must have come from tissue cells, implying that during decompensation water moved into the cells.

"These findings do not fit the pattern anticipated in the loss of edema resulting from initial sodium retention; they do fit the pattern anticipated in the loss of edema resulting from initial water retention," the author states.

Treatment consisted of bed rest and digitalis. In those patients who did not respond to this therapy in a satisfactory manner, a mercurial diuretic was employed. Saline cathartics (Phospho-Soda (Fleet) and effervescent sodium phosphate) were used in six subjects with the sodium computed as part of the daily intake.

"The administration of a saline cathartic did not change in any significant way the course of congestive failure in these patients," reports Dr. Miller. Indeed, "recovery . . . was accompanied by loss of body weight (fluid); by a loss of sodium that was less than the weight loss demanded if that weight loss were due to a release of extracellular fluid; and by a reduction of extra cellular fluid volume smaller than the reduction in body weight." He believes that the fluid retaining effect of excessive amounts of sodium has focused investigative attention upon this ion at the expense of other factors which may be operative in the production of edema.

"There is suggestive evidence that the alteration in renal functions in congestive heart failure includes not only disordered sodium filtration and reabsorption, but also an independent fault in the handling of water," he continues.

The conclusion that the edema of congestive heart failure may be the result of an initial retention of water rather than an initial retention of sodium "should in no way be interpreted as a denial of the importance of sodium restriction in the treatment of edematous states, nor of the role of this ion in contributing to the development of edema," says the author. He adds: "Neither should it imply any value to the restriction of water in congestive heart failure. The measurements that have been made in this investigation are of over-all metabolic changes, not discrete measurements of the moment to moment pathogenic changes."

The subjects included two with arteriosclerotic cardiovascular disease, two with cor pulmonale, two with hypertensive cardiovascular disease and one with rheumatic heart disease.

MYTOLON INTRODUCED NATIONWIDE

New York, N. Y.—A new synthetic compound for relaxing muscular spasm in surgery, Mytolon Chloride Solution, has been introduced on a nationwide scale by Winthrop-Stearns, Inc. The drug, which makes deep anesthesia unnecessary for producing muscular relaxation in surgery, is available in vials of 10 cc, containing 3 mg. per cc., with diaphragm stopper. Average initial dose during surgery is from 3 to 9 mg.

Mytolon is administered intravenously with the anesthetic. Molecules of the drug blanket the receptor sites of all voluntary muscles, blocking nerve impulses and producing a relaxing effect which lasts from 15 to 20 minutes. In more than 400 surgical cases it has proven especially effective for operations of long duration.

For many surgical operations and particularly abdominal operations, it is essential to obtain maximum muscular relaxation. This can be brought about to a partial degree through very deep anesthesia. It is, however, generally recognized that there are undesirable side-effects from anesthesia deep enough to produce the most satisfactory muscular relaxation.

Mytolon, which enables the surgeon to operate under light anesthesia, and at the same time affords full muscular relaxation, makes operations shorter, safer and inspection of internal organs more satisfactory. In addition, it shortens the recovery time from anesthesia and diminishes the after-effects of the anesthetic.

It has also been found useful for muscular relaxation during electroshock therapy and is expected to have uses in treatment of convulsions and wherever an abnormal increase in muscle tone is involved.

Most significant advantages of the new synthetic drug over the natural curare alkaloid compound, known as d-Tubocurarine, according to company literature, are that Mytolon does not produce such side effects as paralysis of the autonomic ganglia, bronchial spasms, histamine release, depressing effect on the heart and falling blood pressure or shock. The autonomic ganglia are important relay stations in the control of many vital body functions and protective reflexes.

The drug also obviates the necessity of obtaining crude curare which comes from the jungles of the Amazon. Chemically, Mytolon is 2,5-bis-(3 diethylaminopropylamino)-benzoquinone-bisbenzylchloride. It is a red crystalline solid.

Sir Walter Raleigh introduced curare in Europe in 1595 and medical science has tried for centuries to synthesize the drug. Mytolon is the newest synthetic curare-like compound developed by scientists at the Sterling Winthrop Research Institute.

The initial dose of Mytolon is generally 6 mg. and satisfactory relaxation is maintained by administering supplemental doses of the drug. Mytolon is especially effective for operations of long duration.

BULK LAXATIVE TABLETS MADE MORE EFFECTIVE

A balanced combination of bulk laxatives has been found to have 87 per cent more moisture-retaining properties per tablet than plain methylcellulose tablets, in a study of human subjects reported by Dr. Maurice L. Tainter, director of the Sterling-Winthrop Research Institute, and his associates in *Gastroenterology* (January, 1952).

Because of the increased water-absorbing properties of the blended formulation, Dr. Tainter pointed

out, fewer tablets per day need to be taken and greater effects are obtained from a given tablet intake.

The balanced formulation contains methylcellulose and refined psyllium seed. It was recently introduced commercially by Winthrop-Stearns Inc. under the trade name Mucilose Compound Tablets.

In 1943, Dr. Tainter first called attention to methylcellulose as having properties making it suitable as a colloid laxative and a substitute for vegetable gums. It has since been accepted as a valuable addition to a well-ordered program for the medical care of patients with obstinate constipation. In addition to its many pharmacological properties, it has a high degree of chemical uniformity and can be readily compressed into tablets.

A combination of psyllium and methylcellulose should have advantages from the sponge-like taking up and holding of water by the psyllium gum, added to the thin, demulcent, viscid liquid formed by the methylcellulose dispersed in the liquid contents of the intestines. Such a balanced formulation, which utilizes the therapeutic merits of two of the leading bulk laxative agents, should be a definitely noticeable improvement over a simple methylcellulose preparation.

Figures cited in the report in *Gastroenterology* established that the compound formula has an enhanced laxative power which permits either greater effects from the full nine tablet dosage regime or the same degree of effect as with plain methylcellulose tablets, but in a smaller daily dose.

A. H. ROBINS CO.

A grant in aid of a clinical research project in industrial medicine, involving arthritic and spastic conditions, has been made by the A. H. Robins Company, Inc., of Richmond, Virginia.

The study will be set up with Dr. Frank Barden, Medical Director of the Saco-Lowell Shops of Biddeford, Maine, as coordinator, and with the participation of four physicians and surgeons in general practice; Drs. Kenneth J. Cuneo, Paul S. Hill, Jr., Robert S. LaFond and William F. Mahaney.

By this collaboration, illnesses frequently encountered in industry can be followed through the stages of continuing treatment by the employee's own doctor, at home and Webber Hospital in Biddeford, it was pointed out by Dr. William R. Bond, Clinical Director of the Robins Company.

The Saco-Lowell Shops, manufacturers of textile machinery, employ about 4,750 persons at plants in Biddeford and Sanford, Maine, and Charlotte, North Carolina.

Dr. Barden said subjects will be selected from several hundred employees suffering from arthritis or various spastic conditions.

In arthritis, therapy with salicylates and Pabalate will be compared. For spastic complaints, belladonna will serve as a control in investigating the results obtained with the antispasmodic, Donnatal.

Observations are to continue for six months. They will be facilitated by X-ray and laboratory work already performed under group and individual insurance plans and supplemented by additional tests as indicated.

THE AMERICAN CONGRESS OF PHYSICAL MEDICINE

The 30th annual scientific and clinical session of the American Congress of Physical Medicine will be held on August 25, 26, 27, 28 and 29, 1952 inclusive, at The Roosevelt Hotel, New York, N. Y. Scientific and clinical sessions will be given on the days of August 25, 26, 27, 28 and 29. All sessions will be open to members of the medical profession in good standing with the American Medical Association. In addition to the scientific sessions, annual instruction seminars will be held. These lectures will be open to physicians as well as to therapists, who are registered with the American Occupational Therapy Association. Full information may be obtained by writing to the American Congress of Physical Medicine, 30 North Michigan Avenue, Chicago 2, Illinois.

RONIACOL

Nutley, N. J.—Roniacol Tartrate 'Roche,' the potent, well-tolerated vasodilator, is now available in new large-size bottles of 1000 tablets, as well as in bottles of 100 and 500. In a recent clinical study (New York State Journal of Medicine, *51*:1303, 1951), Roniacol proved to be more effective as a vasodilator in arteriosclerosis obliterans than other drugs in common use. Other clinical studies have demonstrated the usefulness of Roniacol in various vasospastic disorders, including some cases of angina pectoris.

Chemically, Roniacol Tartrate is the tartaric acid salt of beta-pyridylcarbinol (the alcohol corresponding to nicotinic acid).

"Those interested in the First International Congress of the International Diabetes Federation to be held at Leyden, Netherlands during the second week of July, are kindly requested to apply for a prospectus to Dr. Elliott P. Joslin, Honorary President of the American Diabetes Association, 81 Bay State Road, Boston 15, Massachusetts.

Completed application forms should be in the possession of the Executive Secretary at the Hague on or before April 1, 1952."

U. S. A. F.

The United States Air Force has announced a program whereby commissions will be offered to young men and women practicing in all fields of medicine and in all allied specialized vocations.

The list of vocations includes doctors of preventive medicine, gastroenterologists, obstetricians, gynecologists, allergists, anesthesiologists, ophthalmologists, otorhinolaryngologists, neurologists, internists, general and orthopedic surgeons, radiologists, oral surgeons, periodontists, prosthodontists, medical supply and medical equipment maintenance specialists, sanitary engineers, clinical laboratory technicians, general duty and anesthetist nurses, dieticians, and physical therapists.

Each classification has a different set of requirements for each grade from second lieutenant through the higher grades. The First Air Force has set up clerical facilities for promptly answering all queries concerning these commissions. Inquiries should be directed to the Air Surgeon, Headquarters, First Air Force, Mitchel Air Force Base, New York.

It is requested that the opportunities offered under this program be brought to the attention of all

qualified individuals. Your assistance in implementing this program will be deeply appreciated.

MISSING MINERALS REPLACED

Studies showing a lack of various elements in some foodstuffs suggest faulty food preparation or growth in deficient soil. Some of these mineral elements are no less essential than vitamins, with which they are interrelated in metabolism. Of the many trace elements found in animal tissue, six are believed to be essential for man: iron, copper, iodine, manganese, cobalt, and zinc. Still others may also be important to health.

The exact role of trace elements in nutrition has not been completely defined, but it now appears desirable to ensure their intake in a manner similar to that of vitamin supplementation. Accordingly, Eli Lilly and Company has recently announced a new compound, 'Mi-Cebrin' (Vitamin-Mineral Supplements, Lilly), which supplies, in tablet form, ten appropriately selected minerals in addition to all eleven essential vitamins. The regular use of this integrated nutritional supplement should be helpful in sustaining a healthy existence, continued vigor, efficiency.

THE EIGHTH ANNUAL MEETING OF THE AMERICAN COLLEGE OF ALLERGISTS

The next annual meeting of The American College of Allergists will be held this year at the William Penn Hotel in Pittsburgh, Pennsylvania, on April 7-8-9. The College is offering an unusually practical program for its fellows, members and guests.

In addition to 20 addresses on general topics and special scientific investigations, there will be round tables at luncheons and sectional meetings devoted exclusively to the psychosomatic aspects of the allergic patient, allergy in infants and children, allergic manifestations in the skin, as well as those seen in the eye, ear, nose, and throat.

An innovation for meetings of allergists will be a session devoted to the problems of the allergic patient as met in modern industrial medicine. All reputable physicians are welcome to attend. For more particulars, write the College, La-Salle Medical Building, Minneapolis 2, Minnesota.

GRADUATE INSTRUCTIONAL COURSE IN ALLERGY

On April 4-5-6, 1952, at Pittsburgh, Pennsylvania, The American College of Allergists will offer an instruction course in allergy. To insure complete coverage, the college has called in some 60 well known authorities in the field to give addresses, clinical talks and demonstrations. The program has been designed for physicians in other fields of practice, especially those in general practice, that they may learn to recognize and manage the allergic component in the complaints of their patients. For further information and a copy of the program, write the office of The American College of Allergists, La-Salle Medical Building, Minneapolis 2, Minnesota.

E. Clairborne Robins, president of the A. H. Robins Co., Inc., of Richmond, Va., has been elected to head the Richmond Chamber of Commerce for 1952.

In assuming the presidency for the coming year, Mr. Robins pledged that the Chamber's program for the development of a greater industrial Richmond would be vigorously pushed.

Mr. Robins recently evidenced his personal belief in the city's future when he announced plans for a new $1,000,000 pharmaceutical manufacturing plant, to be constructed on a 10-acre site in a rapidly growing Richmond industrial area.

Active in civic affairs in his home community, Mr. Robins is a director of The Richmond Rotary Club, a trustee of The University of Richmond, and president of the alumni association of The Medical College of Virginia.

THE PENNSYLVANIA STATE COLLEGE SCHOOL OF HOME ECONOMICS

Dr. Grace M. Henderson, Dean of the School of Home Economics at The Pennsylvania State College, announces that Dr. Miriam E. Lowenberg, consultant in nutrition at the Mayo Clinic, Rochester, Minn., has been appointed professor and head of the Department of Foods and Nutrition. The appointment becomes effective February 1, 1952.

Dr. Lowenberg replaces Dr. Eva D. Wilson, who has been serving as head of the Department on a part-time basis for the past year.

From 1927 to 1941, Dr. Lowenberg taught foods and nutrition at Iowa State College. Later she served as chief nutritionist for the Kaiser child service department of the Kaiser Co., Portland, Ore., and as nutritional supervisor for the Rochester Child Health Institute before taking the Mayo Clinic position.

Dr. Lowenberg has conducted research on the reactions of nursery children to texture in vegetables, the relation of diet to gain in weight in infants, and on the diets of pregnant women. She is also the author of two books, "Food for the Young Child," and "Your Child's Food," and has written extensively for professional and popular magazines.

Dr. Lowenberg received her bachelor's degree in philosophy at the University of Chicago, her master's degree in science at Iowa State College, and her doctor's degree in philosophy at the State University of Iowa.

Dr. Lowenberg is a member of numerous professional and honorary organizations including:

American Dietetic Assoc., member of Advisory Board
American Home Economics Assoc., Chairman of Social Welfare and Public Health Department
National Assoc. for Nursery Education, member Child Health Committee and the Well Child Conference Committee
American Public Health Association
Sigma Xi
Sigma Delta Epsilon
Phi Gamma Mu
Eugene Field Society for Writers
Omicron Nu (National President)

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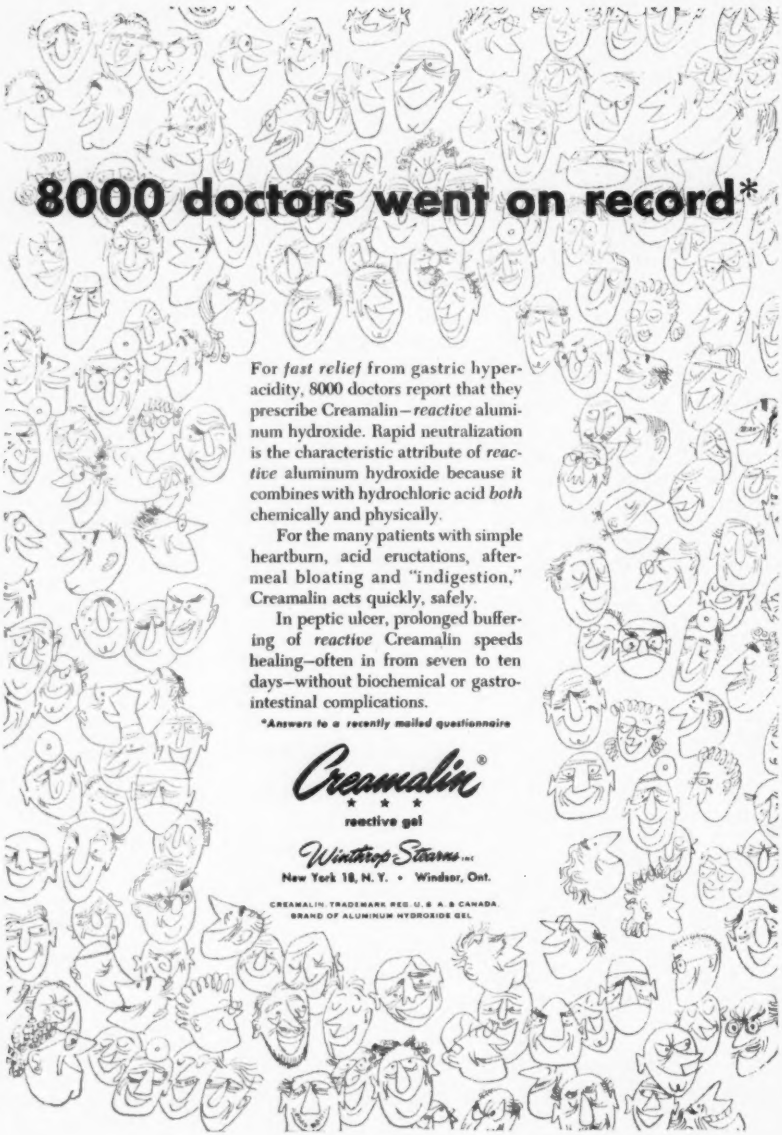

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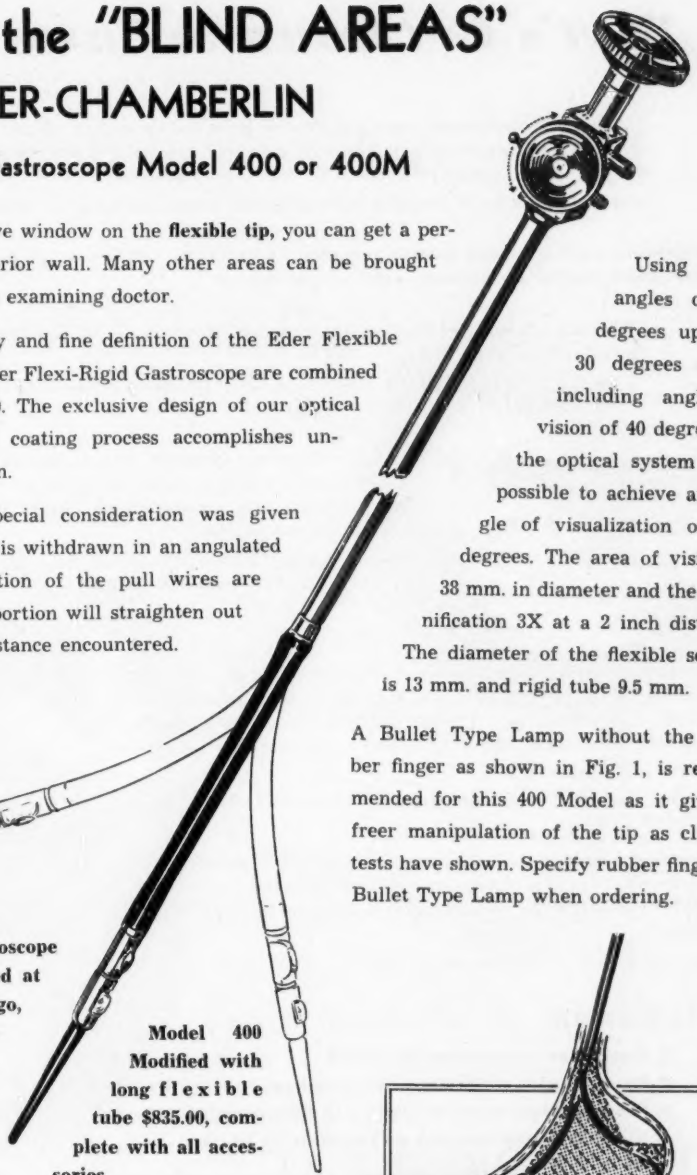


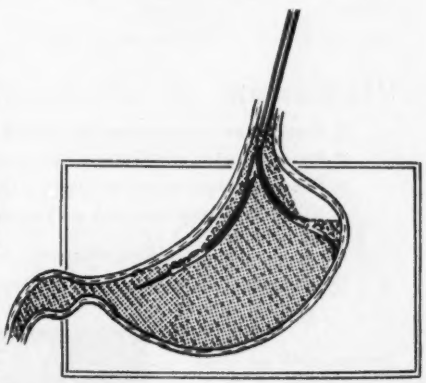
Using both angles of 30 degrees up and 30 degrees down including angle of vision of 40 degrees of the optical system it is possible to achieve an angle of visualization of 100 degrees. The area of vision is 38 mm. in diameter and the magnification 3X at a 2 inch distance. The diameter of the flexible section is 13 mm. and rigid tube 9.5 mm.

A Bullet Type Lamp without the rubber finger as shown in Fig. 1, is recommended for this 400 Model as it gives a freer manipulation of the tip as clinical tests have shown. Specify rubber finger or Bullet Type Lamp when ordering.

Fig. I ⟶

Eder-Chamberlin Gastroscope Model No. 400 is priced at $750.00, F.O.B. Chicago, complete with accessories and attractive leatherette carrying case.

Model 400 Modified with long flexible tube $835.00, complete with all accessories.



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"Although in experimental ulcers both the acid factor and the mucosal resistance factor are concerned, we have examples in which the acid factor predominates and others in which a decrease in the defensive properties of the mucosa predominates."*

*Peptic Ulcer. A. C. Ivy, M. I. Grossman and W. H. Bachrach, Blakiston Publishing Co., Phila., 1950.

Comprehensive therapy—whole duodenal substance, VIODENUM—provides an effective natural antacid plus factors which stimulate the mechanisms of repair and defense.

"Viodenum . . . increased the total volume of gastric secretion . . ." yet "Viodenum decreased the free acid . . ."*

*S. Krasnow, F. Steigmann and L. L. Hardt, Comparison of Effectiveness of Various Antacids on Gastric Acidity. Am. J. Dig. Dis., 17:342 (1950).

peptic ulcer

Dr. P. J. Raimondi treated 59 proven cases of duodenal ulcer with Viodenum. He states, "A decrease in the annual rate of recurrence of symptoms was observed in patients with the highest frequency of exacerbations prior to treatment."*

*P. J. Raimondi, Treatment of Duodenal Ulcers with Desiccated, Defatted Duodenal Powder. Permanente Foundation Med. Bull., 8:4 (October), 1950.

Dr. Garnett Cheney treated 30 cases of ulcerative colitis. He states that Viodenum offers "... great promise in effecting a complete remission and possibly even a clinical cure . . . whole duodenal substance or Viodenum apparently promotes healing of the bowel by supplying some anti-ulcer factor . . ."*

*Medical Management of Gastrointestinal Disorders. Garnett Cheney, Yearbook Publishers, 1950.

ulcerative colitis

"Duodenal substance (Viodenum) was administered to 35 patients . . . the results obtained in 85% of the patients were very favorable . . . Viodenum may be considered a very valuable aid in the therapy of chronic ulcerative colitis."*

*M. H. Streicher, J. Lab. Clin. Med. 33, 1633 (1948).

Viodenum, *the comprehensive approach:*

1. **Provides an effective natural antacid.**
2. **Provides factors which stimulate the mechanisms of repair and defense.**
3. **Provides natural mucin to soothe and protect irritated mucosa.**
4. **Stimulates gastric secretion yet decreases the free acid.**

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dren coming to autopsy from the Harriet Lane Home of the Johns Hopkins Hospital between 1926 and 1942.

The study may remain unique for some time because of the difficulty of collecting comparable material now that the number of children dying of acute infectious disease has been sharply cut by chemo-therapeutic agents.

Reported by Richard H. Follis, Jr., Edwards A. Park and Deborah Jackson, it forms part of a larger analysis, still under way, of the effects of specific and nonspecific factors on skeletal tissue.

The unsuspected amount of severe vitamin C deficiency encountered at certain age levels leads the authors to raise this question:

May not the general prevalence of scurvy in infants be higher than we are accustomed to expect, in view of the relatively few instances that reveal themselves clinically, compared with the much larger number disclosed by post mortem examination of the bones under the microscope?

Omitting doubtful cases, 69 instances of scurvy were found among this consecutive group of 1,303 infants, ranging in age from the first day to the end of the second year. In only six cases had a definite diagnosis of scurvy been made clinically. The disease was not sufficiently advanced in some instances to give signs of its presence during life; in others, it was confounded with rickets. Insufficient weight in the authors' opinion, had been given to histories of prolonged vitamin C deficiency.

The greatest number (85.5%) of cases of scurvy occurred from the fifth through the eleventh month, when the store of vitamin C from the maternal organism may be depleted, when there is tremendous growth activity and before the changed feeding habits of the second year have been introduced. In this group, approximately 17 percent of the infants exhibited the histological signs of scurvy.

This age group is analyzed in terms of feeding history. Among infants receiving at least some breast milk all their lives, no cases of scurvy were encountered at autopsy. The disease was found in 32% of those fed cow's milk alone and in 10% of those fed first by breast and later by cow's milk. Over half the infants with scurvy had received no supplement vitamin C whatever. Race appeared to play no role in the development of scurvy.

Absolute scorbutus is virtually never seen in human material. Where varying amounts of vitamin C were given, there were evidences of healing. An interesting controlled study of healing was provided by twins, 11 months old when admitted to the hospital with severe burns. One died shortly, with marked scurvy found at autopsy. The other child was intensively treated, dying a month later of sepsis and meningitis. The scurvy was completely healed, yet abundant evidence of its preexistence could be found.

This initial report appeared as *The Prevalence of Scurvy at Autopsy During the First Two Years of Age, Bulletin of the Johns Hopkins Hospital, 87:569-591 (December) 1950.*

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Niemiro, B. J.: Delayed Healing in Pilonidal Cyst Wounds. Abstracted from Journal Lancet, Sept. 1951.

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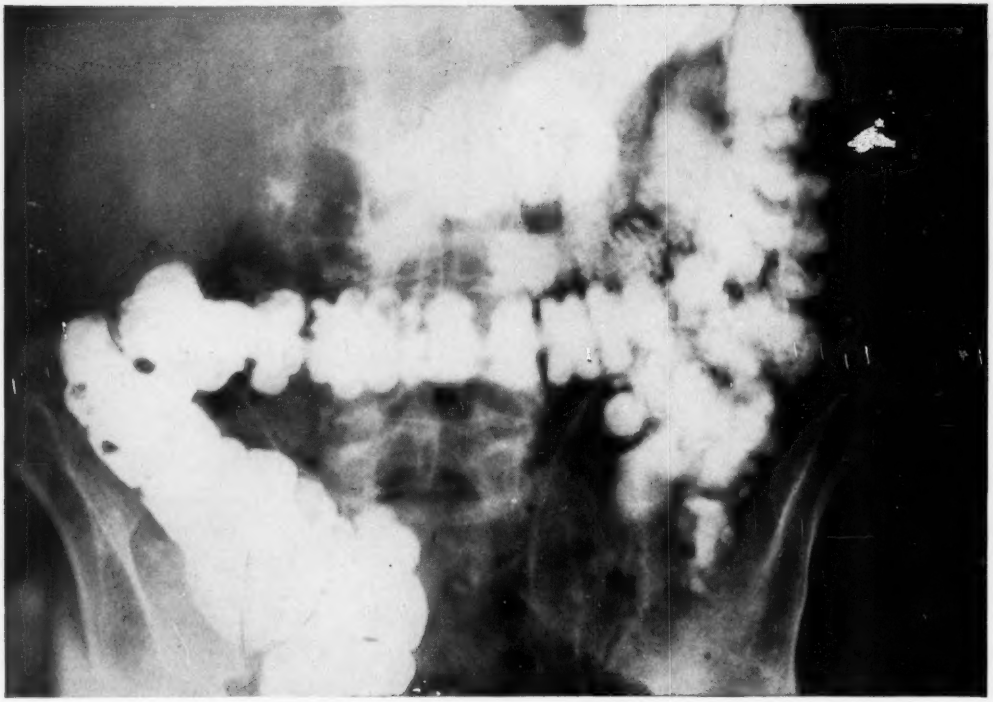

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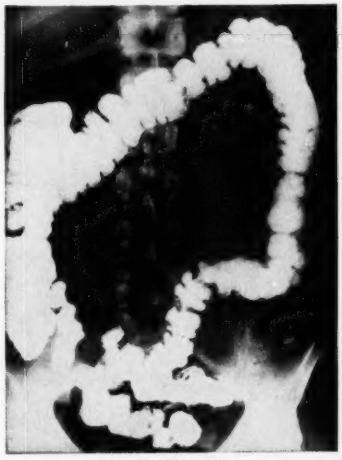

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